The Pharmacokinetics and Pharmacodynamics of Kanamycin and Capreomycin in Patients with Drug Resistant-Tuberculosis and the Relationship between Hearing Levels: A Feasibility Study

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Abstract

Individuals respond differently to medication as a result of their genetic inheritance. These differences can result in the under- or over-dosing of medication, which may affect the efficacy or in the case of aminoglycosides (kanamycin) and polypeptides (capreomycin), result in toxicity. In South Africa, administration of the standardised Drug Resistant - Tuberculosis (DR-TB) medication regimen is simplified across four weight bands. These bands accommodate the formulations available in the country while complying with international requirements for minimum, maximum and average dose per kilogram. There is a dearth of information on the ideal concentration, pharmacokinetics, and pharmacodynamics of kanamycin (KM) and capreomycin (CM) in patients with DR-TB and relationship of this on hearing levels. Thus, this study aimed to establish the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels.

This feasibility study employed a prospective, cross-sectional, exploratory, descriptive and case series research design. A total of 22 participants (mean age 33.78 years, ±7.3) participated in this multi-site study at Helen Joseph (HJH) and South Rand Hospitals (SRH). The majority of the paryicpants were females (68%, *n*=15). Participants underwent audiological (otoscopy, tympanometry, ultra high frequency DPOAEs, ultra high frequency pure tone audiometry) and pharmacological assessments at baseline and every two weeks for the first three months of treatment. Creatinine clearance was measured, and the overall outcome of treatment was evaluated in relation to the pharmacokinetics.

Results revealed high-frequency hearing loss with both kanamycin and capreomycin, specifically in the ultra-high frequencies (9kHz to 16kHz). Clinically significant ultra-high frequency loss noted was with pure tone audiometry from week four after the initiation of

treatment, and from week six in the high frequencies (6kHz to 8kHz). Pharmacokinetic measurements showed erratic levels of kanamycin and capreomycin, with considerable differences among individuals, specifically with the peak readings. Mean peak levels for kanamycin were within the target range yet were subtherapeutic for the capreomycin participants. Kanamycin also correlated to more reduced kidney function when compared to capreomycin. Participants' culture converted within the first two months from baseline, however, long-term culture results are unknown. Trough levels were also below 10 μg/ml and not within a toxic range, despite the hearing loss detected.

This research identified many challenges with regard to establishing the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels. Participant enrolment was poor, with high attrition. This study also highlighted the need for a standardised ototoxicity monitoring protocol designed for this population which led to the development of 'Ototcalc': an ototoxicity calculator in the form of a mobile application designed to assist healthcare professionals in the classification of significant ototoxicity as well as with management recommendations. With the considerations identified in this study to further enhance the feasibility, the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin are recommended for further exploration in relation to toxicity and efficacy with a larger sample, combined with the use of 'Otocalc'.

Keywords: Drug Resistant-Tuberculosis, Ototoxicity, Pharmacokinetics, Pharmacodynamics, Kanamycin, Capreomycin, Otocalc

Declaration

I, Cara Hollander, hereby declare that this submission is my own original work and that the assistance which I have received is detailed in the Acknowledgments of this report. To the best of my knowledge and belief, it contains no material which has been accepted for the award of any other degree of diploma at any other university or other institute of higher learning, except where due acknowledgement has been made in the text. I am responsible for the study and conclusions reached.

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Signed:

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ADA	Adenosine DeAminase
AUC	Area under the curve
ABR	Auditory Brainstem Response
ART	Anti-Retroviral Therapy
ASSR	Auditory Steady State Evoked Response
CDC	Centre for Disease Control
CHRU	Clinical HIV Research Unit
C_{max}	Concentration at the time the drug administration is completed
C_{min}	Concentration at the end of dosing interval
CrCl	Calculation of the Creatinine Clearance
DALYs	Disability-Adjusted Life Years
dB	Decibels
DPOAE	Distortion Product Otoacoustic Emission
DR-TB	Drug-Resistant Tuberculosis
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastro-Intestinal
HFA	High-Frequency Audiometry
HJH	Helen Joseph Hospital
ICF	International Classification of Functioning, Disability and Health
IM	Intramuscular

IV	Intravenous
k_e	Elimination Rate
LAM	Lipoarabinomannan
LC-MS	Liquid Chromatography-Mass Spectrometer
MDR-TB	Multidrug-Resistant TB
MET	Mechanoelectrical Transducer
MIC	Minimum Inhibitory Concentration
MTC	Mycobacterium Tuberculosis Complex
NCI CTCAE	Cancer Institute Common Terminology Criteria for Adverse Events
NDoH	National Department of Health – South Africa
NSP	National Strategic Plan
NTCP	National TB Control Program
OAE	Otoacoustic Emissions
OHC	Outer Hair Cells
PAS	P-Aminosalicylic Acid
PCR	Polymerase Chain Reaction
PTA	Pure Tone Audiometry
QA	Quality Assurance
QALYs	Quality-Adjusted Life Years
ROS	Reactive Oxygen Species
Rpf	Resuscitation-promoting factors
RR-TB	Rifampicin Resistant TB
SANTA	South African National TB Association
SFOAE	Stimulus Frequency Otoacoustic Emissions
SC	Sub-cutaneous

SMU	Sefako Makgatho Health Sciences University
SNR	Signal to Noise Ratio
SPL	Sound Pressure Level
SRH	South Rand Hospital
T1/2	Half-life
TB	Tuberculosis
TEOAE	Transient Evoked Otoacoustic Emissions
TDM	Therapeutic Drug Monitoring
UHFA	Ultra-high Frequency Audiometry
Vd	Volume of Distribution
WHO	World Health Organisation
XDR-TB	Extremely Drug-Resistant Tuberculosis

Definition of Terms

Absorption: Absorption of a drug refers to the transfer of the drug from the site of administration to the bloodstream via one of several procedures (Clark, Finkel, Rey et al., 2012; Atkinson, Huang, Lertora et al., 2012). The drug absorption from the site of administration allows the entry of the therapeutic agent into the plasma.

Aminoglycoside: Aminoglycosides are a well-known and successful class of antibiotics (Huth, Ricci & Cheng, 2011).

Cochleotoxicity: Cochleotoxicity is the toxic damage to the cochlea; initially occurring to the outer hair cells at the basal end of the cochlea. Here the high frequencies are transduced, and thus cochleotoxicity initially affects the ability to hear high-frequency sounds. With prolonged exposure to the ototoxic drug, impairment proceeds to the apical end of the cochlea which is responsible for the processing of low-frequency sounds (Peterson & Rogers, 2015).

Disability-Adjusted Life Years (DALY): The DALY is primarily a measure of disease burden as it weights the disability to the loss of functioning and it takes the age, the origin of disability as well as the quality of life weights into account (Sassi, 2006).

Distribution: Distribution is the method by which a drug reversibly leaves the bloodstream and enters the interstitium and intracellular fluids (Clark et al., 2012). Four main factors are under consideration, namely; blood flow, capillary porousness, the degree of affixing of the drug to the plasma and tissue proteins and the volume of distribution (Clark et al., 2012).

Excretion/Elimination: Excretion or elimination refers to the way the drug leaves the body. Elimination of drugs from the body requires the drugs to be satisfactorily polar for effective elimination. As the drug enters a system, elimination begins via one or more of the three main routes of elimination namely; hepatic metabolism, elimination in bile and elimination in

urine. Excretion of the drug takes place via a number of methods; the most important process is through the kidney and urine (Clark et al., 2012).

Metabolism: Metabolism refers to the process where the drug may be bio-transformed by metabolism of the liver or other tissues. The drug and its metabolites are subsequently eliminated from the body in urine, bile or faeces (Clark et al., 2012).

Multidrug-Resistant TB (MDR-TB): MDR-TB is TB resistant to two first-line drugs: isoniazid and rifampicin (WHO, 2015).

Mycobacterium Tuberculosis Complex (MTC): There are five closely-related mycobacterium species, also known as the MTC, which can cause TB in humans or other living things (Addo et al., 2007). The MTC comprises of Mycobacterium, Mycobacterium africanum, Mycobacterium microti, Mycobacterium canetti and Mycobacterium tuberculosis (Addo et al., 2007).

Ototoxicity: Ototoxicity is defined as a toxic reaction to medication causing damage to the inner ear which often results in hearing and/or balance difficulties (Frymark et al., 2010).

Pharmacodynamics: Pharmacodynamics describe what a drug does to the body and the stimulus of drug concentrations on the degree of the response (Clark et al., 2012).

Pharmacokinetics: Pharmacokinetics refer to what the body does to the drug. It includes aspects such as absorption, distribution, metabolism, and elimination (Clark et al., 2012).

Quality-Adjusted Life Years (QALY): The QALY calculation is based on a multi-attribute theory where utility independence between life years, health status, constant proportional trade-off and risk neutrality on life years are considered, QALYs are used in many cost analysis situations (Sassi, 2006).

Rifampicin Resistant TB (RR-TB): RR-TB includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance

(WHO, 2015). Phenotypic or genotypic means, with or without resistance to other anti-TB drugs detect RR-TB.

Therapeutic Drug Monitoring (TDM): TDM is the clinical practice of measuring particular drugs at chosen periods to maintain a persistent concentration in a patient's bloodstream. TDM optimises individual dosage regimens (Kang & Lee, 2009).

Tuberculosis (TB): Tuberculosis is a contagious, potentially lethal airborne disease (National Department of Health – Republic of South Africa, 2011) caused by mycobacteria; a bacterium of a group of acid-fast bacteria are highly pathogenic organisms (Hatta et al., 2010). The lungs (pulmonary TB) are usually affected, but other sites within the body (extra-pulmonary TB) can however also be affected (WHO, 2015).

Vestibulotoxicity: Vestibulotoxicity is the ability of a substance to destroy or damage the structures and function of the labyrinthine hair cells and their connections through the eighth cranial nerve to the central nervous system (Selimoglu, Kalkandelen & Erdogan, 2003).

Chapter 1: Background and rationale

This chapter introduces the background and rationale for this study. It then details the outline of the thesis with all the chapters and outlines the contents within these chapters.

1.1. Background

Drug-resistant tuberculosis (DR-TB) is becoming increasingly common in South Africa. In 2015 the incidence of new tuberculosis (TB) patients was 10.4 million cases worldwide, with South Africa being one of the six top countries which together account for 60% of the new cases. It is hypothesised that the increase is due to resistance to at least isoniazid and/or rifampicin; two bactericidal drugs used as part of first-line treatment in the fight against TB. As per the 2014 South African National Department of Health (NDoH) guidelines, the treatment for DR-TB involves the use of aminoglycosides and other polypeptides to preserve the life of individuals diagnosed with DR-TB.

Aminoglycosides and some polypeptides are known to be toxic to individuals (Bardien, et al., 2009). Aminoglycosides, such as kanamycin, are inhibitors of prokaryotic protein synthesis at commonly accepted therapeutic concentrations. However, it may also affect the protein synthesis of cells at larger concentrations, leading to toxicity, such as ototoxicity, vestibulotoxicity and/or nephrotoxicity (Touw, Westerman & Sprij, 2009). The toxicity profile of capreomycin, an antimicrobial cyclic peptide particularised by Streptomyces Capreolus, is similar to that of aminoglycosides (Peterson & Rogers, 2015). The use of capreomycin in treating TB is an alternative to kanamycin and amikacin in the treatment of DR-TB (Duggal & Sarkar, 2007). The prevalence of cochlear damage due to aminoglycosides ranges from 7 to 90% (Petersen & Rogers, 2015). This variability could be

due to a potential of underreporting, as well as the lack of distinct parameters for examining ototoxicity (Edson & Terrell, 1991; Petersen & Rogers, 2015).

Nevertheless, in South Africa, the administration of the standardised regimen of DR-TB is simplified and implemented across four weight bands. These broad dosage ranges are employed to adjust the formulations available in South Africa while conforming to the international criteria regarding the minimum, maximum and average dose per kilogram (NDoH, 2011). However, individual patients have their own optimal target concentration based on the susceptibility of the microorganism, co-administered anti-bacterials, immune status and co-administration of other nephrotoxic or ototoxic drugs (Touw et al., 2009). These individual differences can result in an under- or over-concentration of the medication, which may then affect efficacy, or result in toxicity of treatment (Touw et al., 2009). Patients taking kanamycin or capreomycin for DR-TB should not be exposed to any greater risk of toxicity than is justified by the need for the drug, nor obtain any less of the drug that is minimally needed for its effect. Therefore, it is evident that knowledge of the antimicrobial pharmacodynamic properties of medication provides a more rational basis for determination of optimal dosing regimens (Levison & Levison, 2009).

1.2. Rationale for the Study

It is evident that ototoxicity is prevalent in the DR-TB population, specifically in South Africa. Kanamycin and capreomycin are ototoxic and cause irreversible hearing loss which affects the quality of life, as well as social, emotional and occupational well-being. Monitoring and management of ototoxicity is a concern (Khoza-Shangase & Stirk, 2016) and currently no comprehensive protocols for monitoring ototoxicity in this population exist, with various different methods in use in South Africa. There is some evidence for the support of therapeutic drug monitoring (TDM) to reduce ototoxicity, however, more research is

required. Also, interdisciplinary communication with monitoring and management, is rare. The existing ototoxicity grading systems do not seem relevant as they were not developed for this population and frequencies higher than 12.5 kHz, as well as interpretation of audiological results seems to differ between individuals. This difference makes management of the DR-TB difficult for physicians as there are various opinions of a significant change in hearing and thus physicians do not have a combined decision of what is 'significant enough' to motivate for change in the drug regimen of these patients. Lastly, the use of different monitoring protocols and classification of hearing loss also makes it difficult to infer the incidence and prevalence of ototoxicity.

Furthermore, there is a dearth of information on the pharmacokinetics of kanamycin and capreomycin when used to treat patients with DR-TB, a unique and vulnerable population in South Africa. This dissertation postulates that the pharmacokinetics and pharmacodynamics could relate to the levels of ototoxicity of kanamycin and capreomycin in patients with DR-TB. In order to recognise the association between drug levels and ototoxicity, exploration of this is required. Understanding the pharmatherapeutics (pharmacokinetics and pharmacodynamics) of kanamycin and capreomycin in patients with DR-TB could thus assist health care professionals in prescribing and administering the correct dosages. This understanding would include dosage forms and frequency of dosages in order to possibly reduce ototoxic effects and the impact thereof on hearing levels of patients (Touw et al., 2009). This could lead to the further investigation of a contributory relationship of high trough levels of kanamycin and capreomycin to ototoxicity. Subsequently, the possibility of the individualisation of dosages can be explored to reduce this toxicity, specifically ototoxicity. This is especially relevant in patients with DR-TB as post-treatment, many patients are left with disabling hearing loss (Ramma & Ibekwe, 2012; Feldman et al., 2007; Harris et al., 2012). This disability affects their ability to obtain jobs (Hogan,

O'Loughlin, Davis & Kendig, 2009), their social and emotional well-being and ultimately their quality of life (Monzani et al., 2008; Hogan, Reynolds & Byrne, 2013). By reducing ototoxicity, quality of life for these patients will be improved. This will increase social-, emotional- and occupational well-being and decrease the burden of morbidity associated with TB on the society (Monzani et al., 2008; Hogan et al., 2013).

Thus, this research aimed to establish the feasibility of addressing the paucity of information in this field; by determining the pharmacokinetics of kanamycin and capreomycin in patients with DR-TB as well as the relationship between the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin with hearing levels.

1.3. Research Questions

- What is the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship with hearing levels?
- What are the changes in hearing levels in patients treated with kanamycin and capreomycin for DR-TB?
- What are the kanamycin and capreomycin pharmacokinetics in patients treated for DR-TB?
- What is the relationship between kanamycin and capreomycin pharmacokinetics and hearing levels?

1.4. Chapter Outlines

This thesis comprises nine chapters. **Chapter 1** provides a basic orientation to and motivation for the study as well as an outline of the chapters in the study.

In chapters **2**, **3** and **4** the conceptual framework for the study is provided. **Chapter 2** commences with a description of TB and its pathogenesis and then introduces DR-TB with risk factors, the burden of disease as well as the diagnosis and treatment of TB and DR-TB. **Chapter 3** introduces the pharmacology of kanamycin and capreomycin, with explanations regarding pharmacokinetics and pharmacodynamics, design and optimisation of a dosage regimen and lastly the pharmacokinetics of kanamycin and capreomycin. Ototoxicity is introduced in **Chapter 4**. In this chapter, the theories of ototoxicity are discussed, specifically relating to aminoglycosides such as kanamycin and capreomycin. Furthermore, the incidence of ototoxicity is mentioned, as well as ototoxicity specifically in the DR-TB population. Subsequently, ototoxicity monitoring is discussed in detail, as well as the impact that this hearing loss can have on a patient's quality of life.

The methodology of this study is particularised in **Chapter 5** and includes a description of the aims and research design. This chapter contains the study design, study site, study population and the participant sample. It further elaborates on the data collection process; the personnel involved as well as the procedures and equipment involved with the audiological and pharmacological measures. It then continues to discuss the ethical considerations, data management, analysis procedures as well as the reliability and validity concepts.

Chapter 6 provides an overview of the results obtained. Data are organised and analysed so that considerations and conclusions can be drawn regarding the aims of this study.

In **Chapter 7** the findings are discussed in relation to existing literature whilst **Chapter 8** brings forth an outcome of the study in the form of the development of an ototoxicity monitoring protocol and mobile application. **Chapter 9** finally concludes the

thesis with the summary of the findings, strengths, and limitations of the study followed by the implications and recommendations for future research.

The **references** are then presented followed by the **appendices**. The **appendices** supply essential information for the understanding of the data collection and analysis procedures, and thus the replication of the study.

1.5. Summary

This chapter provided the rationale for the study by describing the background information that led to its development, as well as a description of the purpose of the study and research questions. The chapter concluded with an outline of the different chapters by which the aims of the study are described and realised.

Chapter 2: Tuberculosis

The chapter begins with the description of TB and its pathogenesis. DR-TB is subsequently introduced, and pertinent risk factors for TB and DR-TB are discussed. Examinations of the burden of disease follows; regarding incidence, prevalence, mortality, and Disability-Adjusted Life Years (DALYs). The diagnosis of both TB and DR-TB are reviewed in detail followed by the treatment possibilities of TB and DR-TB. Treatment is discussed for both drug susceptible and resistant TB, with the influences of HIV on treatment, the treatment in South Africa, with specific reference to the decentralisation. Lastly, adherence to treatment is discussed.

2.1. Tuberculosis

Mycobacteria, a bacterium of a group of acid-fast bacteria, are highly pathogenic organisms that cause leprosy and TB (Hatta et al., 2010). Tuberculosis (TB) is a contagious, potentially lethal airborne disease (NDoH, 2011). There are five closely-related mycobacterium species, also known as the *Mycobacterium tuberculosis complex* (MTC), that can cause TB in humans or other living organisms (Addo, Owusu-Darko, Yeboah-Manu et al., 2007). The study postulated that the progenitor of this complex arose from a soil bacterium and that the human bacillus may have been derived from the bovine form following the domestication of cattle by humans (Cole et al., 1998). The MTC comprises of *Mycobacterium bovis (M. bovis), Mycobacterium africanum (M. africanum), Mycobacterium microti (M. microti), Mycobacterium canetti (M. canetti)* and *Mycobacterium tuberculosis (M. tuberculosis)* (Addo et al., 2007). *M.tuberculosis*, or TB, is a gram-positive bacterium that contains an additional layer beyond the peptidoglycan that is exceptionally rich in unusual lipids, glycolipids, and polysaccharides.

TB can affect any part of the body. The lungs (pulmonary TB) are typically affected, but other sites within the body (extra-pulmonary TB) can however also be affected (WHO, 2015). Pulmonary TB is the most common form (Sharma & Mohan, 2004) and is also the most infectious. Extra-pulmonary TB is a consequence of the spread of mycobacteria to other organs, most frequently the pleura, lymph nodes, spine, joints, genito-urinary tract, nervous system or abdomen (NDoH, 2014). Not all organs are vulnerable to the TB bacteria. Specific organs and tissues are notably resistant to the multiplication of these bacilli. For example, the bone marrow, liver, and spleen are almost always sowed with mycobacteria, but the unrestrained duplication of the bacteria in these sites rarely occurs.

The multiplication of these mycobacteria in specific organs, specifically in the lungs (pulmonary TB) results from the spreading of droplet nuclei, as discussed in the pathogenesis below.

2.2. Pathogenesis

The pathogenesis and transmission of TB are implicated with a droplet nucleus mechanism (Riley, 1974; NDoH, 2014).

There is some controversy regarding the factors that clarify the prospect of transmission of TB. According to the Centre for Disease Control (CDC, n.d), four factors determine the probability for the transmission of *M. tuberculosis*, namely: (i) susceptibility of the exposed individual, (ii) infectiousness of the person with TB (which is directly related to the number of tubercle bacilli he/she expels), (iii) environmental factors that affect the concentration of *M. tuberculosis* organisms, and (iv) the proximity, frequency and duration of exposure (CDC, n.d).

However, according to the NDoH (2014), three factors establish the probability of transmission of *M. tuberculosis* namely: (i) the amount of TB organism expelled; (ii) the

concentration of TB organisms as well as (iii) the period exposed to contaminated air. The NDoH does not include the environmental factors as per the CDC classification.

The CDC (n.d) discusses that smaller enclosed spaces place an increased risk for transmission, while inadequate confined or general aeration results in deficient reduction or removal of infectious droplet nuclei. The recirculation of air containing infectious droplet nuclei as well as positive air pressure also stands as a risk for infection (CDC, n.d). Although, later in the NDoH guidelines (2014) it mentions that the concentration of these bacilli in the air, which is affected by the volume of space and the aeration, also affects the likelihood of infection (NDoH, 2014). Transmission is highest in dark and poorly ventilated spaces, while direct sunlight kills TB bacteria quickly (NDoH, 2014).

Thus, TB has a complex life cycle, which includes two types of infection, namely primary and post-primary TB (Hunter, 2011).

2.2.1. Primary Infection

Primary infection occurs on first exposure to the TB bacilli from respiratory secretions from a patient with an infection of the respiratory tract (NDoH, 2014). This infection contaminates surrounding surfaces and becomes suspended in the air after coughing, sneezing, spitting and other respiratory acts. These small suspended respiratory droplets evaporate in the air and become tiny droplet nuclei (Riley, 1974). Droplet nuclei are small particles, one to five micrometres (μm) in diameter, containing one to five highly infectious bacilli. These droplets are minute and able to reach the alveolar spaces within the lungs (NDoH, 2014). An infectious dose of TB is only one to two bacilli, yet an infected individual can produce 3000 droplet nuclei and sneeze up to a million droplet nuclei which contain bacilli. The most infectious cases are those with smear-positive pulmonary TB (TB with more than 3000 bacilli), yet smear-negative pulmonary TB (TB with fewer bacilli) cases are less infectious (NDoH, 2014).

After inhalation of the tubercle bacillus in the droplet nuclei, these nuclei transmit down the trachea-bronchial tree and accumulate in a respiratory bronchiole or alveolus (Smith, 2003), normally in the lower part of the upper lobe or upper part of the lower lobe (NDoH, 2014). Here the alveolar macrophages ingest the droplet nuclei that produces a nonspecific response to the bacillus. Other macrophages and monocytes are enticed to the area and create an immune response. This inflammatory area is known as the Ghon focus. Bacilli and antigens drain from the Ghon focus via the lymphatics to the hilar lymph nodes, and together these form the primary (Ghon) complex. The inflammatory response generates the typical picture of caseous necrosis. Within the lymph node, the T-lymphocytes mount a specific immune response and activated macrophages inhibit the growth of the phagocytosed bacilli. This primary focus contains 1 000 – 10 000 bacilli that gradually lose their viability and multiply increasingly slowly. The tubercle bacillus grows slowly, splitting around every 25 to 32 hours within the macrophage (Hunter, 2011; NDoH, 2014).

In addition to the macrophages, dendritic cells play a crucial function in the initial stages of infection since they are better antigen presenters than macrophages and ostensibly play a central role in stimulating T-cells with specific *M. tuberculosis* antigens. As dendritic cells are nomadic, unlike discerned macrophages, they also may play an essential role in the dissemination of *M. tuberculosis* (Smith, 2003). Fibrous scar tissue replaces the inflammatory area in the primary focus, sometimes with calcification, in which the macrophages comprising bacilli are isolated and die (Hunter, 2011; NDoH, 2014).

Extra-pulmonary TB can occur in organs that favour the growth of the TB bacilli such as in the kidneys, bones, and brain (NDoH, 2014). Although it is postulated that *M. tuberculosis* bacilli are unable to increase within this caseous tissue due to its acidic pH, the low availability of oxygen, and the presence of toxic fatty acids, some organisms may remain dormant but alive for decades (WHO, 2015). Thus, extra-pulmonary TB is, therefore,

bacteriologically confirmed or a clinically diagnosed case of TB involving organs other than the lungs, for example, pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones and meninges (WHO, 2015).

Nevertheless, TB is not always transmitted and does not always become infectious. In persons with an effective cell-mediated immunity, the infection may arrest permanently at this point (Smith, 2003). The strength of the host cellular immune response governs whether an infection halts here or progresses to the next stages. This enclosed infection is referred to as latent or persistent TB and can endure during a person's life in an asymptomatic and non-transmissible state. Individuals with dormant TB infection are not infectious, as they do not have repeating bacteria and cannot spread the organism (NDoH, 2014). Also, in some cases, when TB is transmitted, the cellular immunity develops, and macrophages kill the infectious bacilli. Although the bacilli are killed it often results in the formation of the caseous centre in the granuloma, surrounded by a cellular zone of fibroblasts, lymphocytes, and blood-derived monocytes (Smith, 2003).

2.2.2. Post Primary TB or Secondary TB

Post-primary TB / Secondary TB may occur either by *reactivation* of latent bacilli or by *re-infection* (NDoH, 2014).

Reactivation occurs when dormant bacilli, persevering in tissues for months or years after primary infection, start to reproduce. This may be a reaction to a prompt such as waning of the immune system by HIV infection for example (NDoH, 2014). Wong and Jacobs (2016) discuss that post pulmonary TB cases and almost all transmission of the disease is due to post-primary TB. It differs from primary TB in the genes that modulate susceptibility, clinical presentation, complications and age distribution of hosts. Post-primary TB is typically restricted to the upper lobes of the lungs and does not involve lymph nodes or other organs (Hunter, 2011). Post-primary TB develops mostly in immune-competent adults who gained

immunity earlier in their life from their first *M. tuberculosis* exposure and primary TB (Wong & Jacobs, 2016).

In contrast, *re-infection* occurs when an infectious person exposes a person who previously had a primary infection. Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults. Chest X-rays may show intra-thoracic lymphadenopathy and lung infiltrates (NDoH, 2014). Sputum smears are regularly positive, and there is commonly no intrathoracic lymphadenopathy (NDoH, 2014).

2.3. Further classification of TB

TB is further described and classified as outlined by the Global TB Report (WHO, 2015) and other sources (Pontali, Matteelli & Migliori, 2013; NDoH, 2011).

- **Bacteriologically confirmed case of TB** -A patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid-diagnostic-test (such as Xpert MTB/RIF) (WHO, 2015).
- **Clinically diagnosed case of TB** -An individual who does not match the criteria for bacteriologically substantiated TB but has been diagnosed with active TB by a clinician or other medical expert who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed based on X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory validation (WHO, 2015).
- **New case of TB** -A patient who has never received treatment for TB or has taken anti-TB drugs for less than one month (WHO, 2015).
- **Retreatment case of TB** -A patient who was treated for one month or more with anti-TB drugs in the past. Retreatment cases of TB could be a relapse, treatment again after

the failure of previous treatment, treatment after the loss to follow up and other unknown reasons (WHO, 2015).

- **Drug-Resistant Tuberculosis (DR-TB)** - Strains of TB that are resistant to anti-TB antibiotics (Pontali et al., 2013; WHO, 2015). DR-TB may vary from single drug (DR-TB) to multiple drug resistance (MDR-TB) (Pontali et al., 2013). The Global Tuberculosis Report describes DR-TB according to RR-TB, MDR-TB and Extremely Drug-Resistant TB (XDR-TB) (WHO, 2015). DR-TB can also be described according to **Rifampicin Resistant TB (RR-TB)** which is TB resistant to rifampicin, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance (WHO, 2015). Further**,** **Multidrug-Resistant TB (MDR-TB)** is TB that is resistant to two first-line drugs: isoniazid and rifampicin. For many patients diagnosed with MDR-TB, the WHO advocates treatment for 20 months with a regimen that incorporates second-line anti-TB drugs (WHO, 2015).
- **Extremely Drug-Resistant (XDR-TB)** is resistant to rifampicin, isoniazid and two of the most critical classes of second-line anti-TB drugs, namely a fluoroquinolone (such as oxifloxacin) and an injectable drug (namely amikacin, kanamycin or capreomycin) (WHO, 2015). XDR-TB is a particularly dangerous form of DR-TB (NDoH, 2011). DR-TB, whether RR-TB, MDR-TB or XDR-TB, can be further classified according to the TB treatment history with regard to resistance in new patients, resistance in previously treated patients or resistance levels in re-treatment (NDoH, 2011). The treatment of DR-TB involves second line drugs which are less potent and more toxic than those used for drug-susceptible TB (Pontali et al., 2013).

2.4. Associated Risk Factors

There are several risk factors associated with TB, involving exogenous and endogenous factors. Exogenous factors play the main role in emphasising the advancement from exposure to infection (Narasimhan, Wood, MacIntyre & Mathai, 2013), while endogenous factors are aspects related to the individual (Narasimhan et al., 2013).

2.4.1. Exogenous factors

According to NDoH (2014), MDR-TB is a human-made problem, which is a consequence of human error, which can include either management of drug supply, patient management; including prescription miscalculations and/or patient adherence (NDoH, 2014). This assumption involves the social risk factors as discussed by Zhao, Li, Zhang, Wang and Liu (2012) but does not include other influences such as long-term illness, age, and poverty (Zhao et al., 2012). Conversely, Günther (2014) postulates that MDR-TB strains are being actively transmitted from person to person with accumulative regularity, and not always a direct consequence of human error.

Risk factors can further include the aspects related to the TB itself (exogenous) and the person (endogenous) (Narasimhan et al., 2013). The exogenous features mainly include the bacillary load in the sputum and the proximity of an individual to an infectious TB case (Narasimhan et al., 2013). Correspondingly, endogenous aspects guide in the evolution from infection to active TB disease and are often host related.

Regarding exogenous influences, the risk factor of the bacillary load refers to the concentration of the bacilli in the sputum from the TB case. Thus, a higher concentration of bacilli in the sputum results in a more infectious sputum sample. A high concentration of bacilli (smear positive) in the sputum is more likely to be transmitted than a smear-negative sample with a lower concentration (Narasimhan et al., 2013). Close interactions of infectious

TB cases (including household contacts and caregivers/healthcare workers) are at a higher risk of becoming infected with TB and the expansion of primary active tuberculosis (Narasimhan et al., 2013).

2.4.2. Endogenous factors

Endogenous factors include a more extensive variety of aspects which involve the effects from the individuals. These effects can include immunosuppression such as human immunodeficiency virus (HIV), malnutrition and a young age, as well as, evolving variables such as diabetes, indoor air pollution, excessive alcohol use, use of immunosuppressive drugs, and excessive tobacco smoke (Narasimhan et al., 2013). Socioeconomic and behavioural factors, as well as specific groups such as health care workers, are a factor in the susceptibility of TB infection (Narasimhan et al., 2013).

Malnutrition, (both micro- and macro-deficiency), is another endogenous factor shown to increase the risk of TB because of a weakened immune response. TB disease can itself lead to malnourishment because of declining appetite and changes in metabolic processes. Although there is a link between malnutrition and risk of TB, the specific levels that place one at risk still need identification (Narasimhan et al., 2013).

Furthermore, the presence of diabetes (Type 1 and Type 2 diabetes) also indicates an increased risk for the development of the active TB disease. It is approximated that currently 70% of people with diabetes live in low- and middle-income countries, and the rates are progressively increasing in areas where TB is endemic, including India and sub-Saharan Africa. Diabetes is an endogenous risk factor as it directly prejudices the innate and adaptive immune responses, thereby accelerating the proliferation of TB (Narasimhan et al., 2013).

2.4.3. Additional factors

Other factors that place one at risk of contracting TB include low socioeconomic and behavioural factors, alcohol abuse and indoor air pollution (Narasimhan et al., 2013). People with a low socioeconomic status are at risk for malnutrition, indoor air pollution, alcohol abuse. They are more likely to live in overcrowded and less ventilated spaces as well as are more likely to become infected with HIV. In South Africa, many dwellings are overcrowded, and unhygienic due to poor economic conditions, which increases this risk of infection (Narasimhan et al., 2013).

Some working environments may also put some at risk for indoor air pollution. In developing countries, more than 80% of solid fuels for cooking is used. Firewood or biomass smoke has been recognised previously as a non-aligned risk factor for TB disease. Excessive alcohol consumption places one at an increased risk of alterations in the immune system, specifically in modifying the signalling molecules responsible for cytokine production. The association between tobacco smoke and TB has also been reviewed and shown that smokers have more chance of contracting TB than non-smokers. Also, health workers are at increased risk of exposure to TB (Narasimhan et al., 2013). Lastly, issues with health care systems may increase the risk for transmission of TB. Delays in the diagnosis and treatment initiation place an infected individual at risk of transmitting the disease (Narasimhan et al., 2013).

Apart from the multifactorial process influencing the outcome of the disease, involving both environmental or host-related factors, in conjunction with the actual pathogen, genetic structures may also be affecting this disease progression (Mboowa, 2014). Studies from Canada and Australia have shown that indigenous people or Aborigines are at a higher risk of developing TB than the non-aborigines (Wang, 2000). A study conducted in Canada showed that several aborigines had a gene deletion that may have predisposed them to developing active TB disease (Greenwood et al., 2000). Additionally, Human Leukocyte

Antigen (HLA) alleles are found to be associated with susceptibility and resistance to infectious diseases including TB. A study from various populations throughout the world showed countries further from Africa have lower HLA diversity, indicating possibly African genetic susceptibility to TB (Mboowa, 2014). Furthermore, a susceptibility locus of rs4331426 on chromosome 18q11.2 for TB in the African population has been identified (Mboowa, 2014).

XDR and MDR-TB have the same root cause: negligent case-management and poorly operational public-health services. The magnitude of this public health problem is instigated by incorrect prescription of drug regimens, poor drug quality, erratic drug supply, non-adherence by patients, and inadequate infection control (Van Rie & Enarson, 2006). The deteriorating health care system, in conjunction with the other exogenous and endogenous factors, is specially problematic, as in South Africa, decentralisation of treatment occurs, where patients are treated with an outpatient regimen. These guidelines do not consider the poor living conditions, as many South Africans reside in homes with little or no ventilation as well as factors such as malnutrition, overall health aspects, and alcohol abuse to name a few.

2.5. Burden of Disease

Burden of disease describes the total and cumulative effects of a defined disease with respect to disabilities in a population. These outcomes include health and social aspects as well as costs to society (Kirch, 2008). Burden of disease is measured generally in terms of incidence, prevalence, and mortality (WHO, 2014). It is also often measured with DALYs (Institute for Health Metrics and Evaluation, 2010).

The overall burden of TB has been declining at an annual average of 2.2% (between 2010 and 2011) yet the number of patients with DR-TB in increasing (Heychendorf, Olaru, Ruhwald & Lang, 2014). The poor treatment outcomes also indicate the extent of the burden

of disease. A systematic review was conducted with the aim to synthesise available evidence on treatment outcomes from community-based multi-drug resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) treatment programs. Unfortunately, no data mentioned South Africa. Of this population, 65% of patients had a successful outcome, 15% defaulted, 13% died, and 6% failed treatment for a total of 35% with unsuccessful treatment outcome (Weiss, Chen, Cook & Johnston, 2014). In the research reported in the NDoH guidelines (2011), 71% of patients started DR-TB treatment in 2010. It does not mention success rates of this though. However, in the meta-analysis above, 65% with a successful outcome is not enough. Unfortunately, this study was not able to obtain data regarding the overall outcome of treatment, but it does highlight the considerable burden of TB and DR-TB.

2.5.1. Incidence and Prevalence

In 2015, the global incidence of new TB cases was 10.4 million, of which 5.9 million were men and, 3.5 million were women, and one million were children. The top six countries that accounted for 60% of the new cases were India, Indonesia, China, Nigeria, Pakistan and South Africa. The rate of decline in TB incidence was only 1.5% from 2014 to 2015 worldwide (WHO, 2016b). In 2015, there were an estimated 480 000 new cases MDR-TB cases worldwide and 100 000 RR-TB cases who were eligible for treatment, yet only 12 000 enrolled (20%). In the 2016 WHO TB Report, globally, the MDR-TB treatment success was only 52% (WHO, 2016b).

In 2012, 14 161 cases of MDR-TB were documented in South Africa (Conradie et al., 2014). Günther (2014) writes that in 2012 in SA, 1.8% of new cases and 6.7% of retreatment patients had MDR-TB within an overall estimated TB incidence of 1,000 per 100,000 people. However, the precise global trends of DR- TB incidence and prevalence are currently ill-defined because of inadequate investigation and recognition methods (Günther, 2014). In this

article by Günther in 2014, XDR-TB had been detected in 92 countries and with an average of 9.6% of MDR-TB cases having XDR-TB cases. He further states that there have been publications on totally drug-resistant TB (TDR-TB), where such patients are resistant to all second-line anti-TB medication tested. However, TDR-TB is not yet officially recognised nomenclature.

South Africa has the third highest absolute number of reported incident cases as well as the fifth highest number of estimated prevalent (undiagnosed active TB) cases. After adjusting for population size, South Africa has the highest incidence and prevalence of TB among high burden TB countries (Churchyard et al., 2014). Although the prevalence of TB may be decreasing, the prevalence of DR-TB is increasing.

Earlier, a review by the South African National Tuberculosis Association (SANTA) found that with an approximate population of 41.4 million and an estimated 130,000 TB cases in 1995, South Africa had one of the maximum annual TB incidences (311 per 100,000 populations) in the world. The TB incidence did, however, vary radically by both geographical region and population group (SANTA, 2013). Gauteng was not ranked as a province with a higher incidence of TB, as were the Eastern Cape, Kwa-Zulu Natal and the Western Cape (Kanabus, 2017). Onyenekwu, Zemlin and Erasmus (2014) further reported that that the incidence of TB in the Western Cape is higher than the national incidence rate of 823/100 000 population, at 935/100 000 population (Onyenekwu et al., 2014).

From these 10.4 million cases, 1.2 million were HIV positive. HIV, a prominent risk factor increases the probability to acquire active TB than those with healthy immunity. The NDoH (2011) describes the combination of HIV and TB as a lethal combination, each speeding the progression of the other disease. Worldwide, the proportion of TB cases living with HIV was highest in the African Region (WHO, 2016b). South Africa also has one of the world's most significant TB epidemics driven by HIV. It also has the most substantial

number of HIV-associated TB cases and the second-largest number of diagnosed multidrug-resistant TB cases (after India) (Churchyard et al., 2014). TB is a prominent cause of death among individuals who are HIV infected (NDoH, 2011). Fifty to 60% of HIV positive people infected with TB will go on to develop active disease.

The yearly risk of TB in an HIV positive individual is 10% contrasted to a lifetime risk of 10% in a healthy individual (NDoH, 2014). Globally, according to the TB report (WHO 2016b), in 2015, 55% of TB patients had a documented HIV test result. In the African Region, 81% of TB patients had a recorded HIV test result. The relative number of known HIV-positive TB patients on antiretroviral therapy (ART) was 78% globally. Also, according to this report published in 2016, globally, 15% of TB patients with an HIV test result were HIV-positive (WHO, 2016b).

2.5.2. Mortality

In 1993, the WHO declared TB a global public health emergency (WHO, 2014a). Since 1990, TB mortality has fallen 47%, with most of that improvement taking place since 2000. Between 2000 and 2014, an estimated 43 million lives were estimated to have been saved through correct diagnosis and treatment (WHO, 2015a).

An estimated 1.4 million TB deaths transpired in 2015, and an additional 0.4 million deaths resulting from TB disease among persons living with HIV occurred. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015 (WHO, 2016b).

2.5.3. Disability Adjusted Life Years (DALYs)

The global burden of disease study, conducted in 2010, was a collective project of approximately 500 researchers in 50 countries led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington (IHME, 2010). Global Burden of

Disease serves as a global public to advise evidence-based policymaking and health systems design. Amongst others, the IHME evaluated Disability Adjusted Life Years (DALYs) (IHME, 2010). DALYs quantify both premature mortality and disability within a population. In South Africa, the top three causes of DALYs in 2010 were HIV, diarrheal diseases, and interpersonal violence. TB ranked fifth after lower respiratory infection (IHME, 2010). In a population of 54 490 000 in South Africa, the fifth ranking on the DALY list demonstrates the immense problem of TB and the number of people it affects; in many aspects of their lives.

2.6. Diagnosis of Tuberculosis

Prompt and accurate diagnosis of all forms of TB followed by provision of treatment in line with international benchmarks prevents death and limits ill-health among individuals who develop the disease. It also prevents further spread of infection to others (WHO, 2016b).

Diagnosis of TB and DR-TB requires a comprehensive assessment that includes a comprehensive medical history, physical examination, bacteriological investigations and other adjunctive clinical tests to confirm the diagnosis (NDoH, 2014).

2.6.1. Medical History

A comprehensive medical history is vital to understand the patient's history of TB exposure, infection or disease (CDC, 2016). In addition to general medical history, the clinician should probe areas relating to previous TB infections and current symptoms of TB. Should symptoms be present, the clinician would continue with further enquiries regarding the specificities of the symptoms, as well as if the patient has had contact with a person with infectious TB disease. Equally important is obtaining information on whether the person was diagnosed in the past with latent TB infection or TB disease. Clinicians may be required to

contact other districts or treatment sites regarding previous infection, treatment regimen and known outcome (CDC, n.d). Demographic factors should also be obtained such as country of origin, age, ethnicity, occupation, or racial group as these may increase the patient's risk of exposure to TB infection. Clinicians should further determine if the patient has underlying medical conditions, specifically HIV or diabetes (CDC, n.d; Tattevin et al., 1999).

2.6.2. Physical Examinations

The physical examination is an essential part of the evaluation of any patient (CDC, n.d; NDoH, 2014; Herchline & Amorosa, 2016). Although the physical examination cannot confirm or rule out TB disease, it does provide valuable information about the patient's overall condition, inform the method of diagnosis, and reveal other factors that may affect TB disease treatment, if diagnosed (CDC, n.d; NDoH, 2014; Herchline & Amorosa, 2016).

Specific aspects of identifying patients with possible pulmonary TB would include raised body temperature, increased pulse, and abnormal signs when listening to the chest. Other symptoms of TB and DR-TB can include dyspnoea, haemoptysis and systematic symptoms (fever, chills, night sweats, tiredness, anorexia, weight loss). When listening to the chest, one would listen for crackles in the lung apices to be more pronounced on deep breathing; localised wheezing in local obstructions or pressure; dullness where there is effusion and in chronic disease there may be extensive fibrosis with the trachea pulled to one side (NDoH, 2014). There may also be manifestations unrelated to the site of involvement, including haematological abnormalities, hyponatraemia, and psychological disorders. Extra-pulmonary DR-TB, however, is more difficult to diagnose because it often involves very inaccessible sites (NDoH, 2011). The doctors' medical history and examination would try to identify the above symptoms. (CDC, n.d; NDoH, 2014; Herchline & Amorosa, 2016).

2.6.3. Bacteriological Investigations

Definitive diagnosis can only be attained based on bacteriological investigations. According to the WHO (2014a), among pulmonary TB cases, 58% were bacteriologically confirmed (as opposed to clinically diagnosed) in 2013. The remaining 42% of patients who were not bacteriologically confirmed could result in a false diagnosis with individual's enrolment on TB treatment when not necessary. Furthermore, a low rate of laboratory confirmation reflects an under-diagnosis of true TB cases and contributes in part to the continuing global gap between notified and estimated incident TB cases (5.7 and 9.0 million in 2013, respectively). Also, detection of TB without investigating for drug resistance can lead to ineffective treatment, further development and spread of drug-resistant strains and additional suffering and costs for patients.

All forms of bacteriological TB diagnoses occur by using a variety of bacteriological investigation methods (NDoH, 2014). The diagnostic tests available to confirm bacteriological TB include: (i) Smear Microscopy, (ii) Culture Methods, and (iii) Molecular Methods [Polymerase chain reaction (PCR) based assays: Line probe assay and Xpert MTB/RIF].

Microscopy and culture are still the basis of TB diagnostics. Sputum smear microscopy is the most common method for diagnosing TB worldwide (Desikan, 2013; NDoH, 2014). Sputum smear microscopy entails the examination and observation of the bacilli in sputum samples under a microscope (Desikan, 2013; NDoH, 2014), using either one of two staining methods, namely the Ziehl-Neelsen staining method (NDoH, 2014, Truffot-Pernot & Cambau, 1994) or fluorescent auramine staining method (NDoH, 2014). The staining procedure depends on the ability of mycobacteria to retain these dyes when treated with acid and alcohol solutions (NDoH, 2014).

The use of sputum smear microscopy is controversial. Sputum smear microscopy is fast, inexpensive and requires minimal bio-safety standards (Desikan, 2013; Steingart et al., 2006; WHO, 2014b). However, it is not a sensitive test, particularly in children and people living with HIV as it provides no information on the viability and drug susceptibility of the bacilli. The viability and drug susceptibility were observed in a study published in Stellenbosch, South Africa, where the objective was to assess the use of a sputum register to evaluate the TB diagnostic process and the initiation of TB treatment. TB patients were classified as patients with two positive smears. Over the entire diagnostic process, up to 5% of TB cases were missed (Botha et al., 2008). The sensitivity is grossly compromised when the bacterial load is less than 10,000 organisms/ml per sputum sample. It also cannot distinguish between MTC and non-TB mycobacteria (Desikan, 2013; WHO, 2014b).

Culture methods, in comparison, are more sensitive than smear microscopy as they detect a higher proportion of cases among patients with symptoms (David, Katalinić-Janković, Fattorini & Cirillo, 2016; Desikan, 2013). It allows for the detection of very low numbers of bacilli (approximately 10 bacilli/ml of sputum compared with at least 5000 bacilli/ml of sputum for microscopy) (David et al., 2016). The use of culture tests increases the number of TB cases found by 30–50% (David et al., 2016). Culture tests diagnose extrapulmonary TB, distinguish TB from non-TB mycobacteria and detect treatment failures. Culture testing is also critical for monitoring patients' response to treatment for DR-TB.

Molecular methods have been the recent breakthroughs in TB diagnostics in the past decade, to diagnose TB and DR-TB (WHO, 2014b). In 2010, the WHO endorsed *Xpert®MTB/Rif* (Cephaid, Sunnyvale, USA), a PCR-based diagnostic tool (Günther, 2014). Molecular biology is now becoming more critical in the diagnosis of mycobacteria. It supports culture either by serving as a rapid direct test on specimens or by enabling a rapid and unequivocal species differentiation from culture material. Nucleic-acid-based methods

have primarily displaced the classical methods (Hillemann, Miychell, Drobniewski, 2016). In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard) (WHO, 2014b). Molecular genetic tests offer considerable time advantages in the identification of mycobacteria, enabling a more rapid initiation of resistance tests and specific treatment. Molecular methods are useful tools for the detection and differentiation of mycobacteria from cultures and can have a high specificity and sensitivity. It should be stated, however, that they cannot/should not replace the currently endorsed standard methods of detecting mycobacteria and determining drug-susceptibility patterns. Instead, their use should support the diagnostic work-up. Confirmation of the test results should always be through the use of the standard methods (Hilleman et al., 2016).

In South Africa, there are two PCR technologies available which provide different information that is helpful in the management of TB and DR-TB. They include the *Xpert®MTB/Rif* test using the Gene Xpert (GXP) instrument, which is useful for rapidly diagnosing TB as well as it allows rapid screening for Rifampicin resistance. Results can be available within two hours in the laboratory but only become available within 48 hours in health facilities (NDoH, 2014). In clinical evaluation studies, its sensitivity approaches 100% in smear-positive pulmonary TB patients and 57–83% in patients with smear-negative pulmonary TB (Pontali et al., 2013).

As per the South African guidelines when diagnosing DR-TB rapid testing using Xpert®MTB/RIF, confirmatory drug susceptibility testing for patients with RR-TB, rapid tracing and linkage to treatment and rapid tracing and evaluation of contacts is suggested (NDoH, 2014). Gene Xpert is the method most commonly used in South Africa.

Line probe assay is the second molecular test that can be performed on all respiratory specimens and other specimens where the detection of rifampicin resistance in MTB is the primary purpose of the investigation (Hilleman et al., 2016). This is useful for drug resistance

confirmation and detects resistance to both Rifampicin and Isoniazid. Line probe assays is specific for MTB complex and can differentiate MTB from other mycobacteria. Line probe assays can only be performed on smear positive or culture positive sputum specimen (NDoH, 2014).

Where molecular tests, such as the GeneXpert are available, culture may still be required for HIV positive patients where TB is suspected yet have a negative GeneXpert test (NDoH, 2014) and RR-TB cases, where testing for another drug resistance is necessary (NDoH, 2014).

There are a few other bacteriological tests that can be used in conjunction with the methods mentioned above but should not be used in isolation as a diagnostic test. These tests include: (i) Interferon gamma Release Assays (blood tests that detect MTB infection but cannot distinguish latent TB from active TB), (ii) blood culture (may be used to detect MTB and other species of mycobacteria in HIV-infected patients; especially those with low CD4 count), (iii) TB LAM (detects lipoarabinomannan antigens in urine - further studies are however required to determine the role of this test), (iv) histological examination (can be conducted on a tissue specimen, but this is not considered to be bacteriological confirmation of disease) and (v) the Tuberculin skin test (limited value in clinical work as the test shows hypersensitivity to proteins of the TB bacillus, as a result, either of infection with M. tuberculosis or induced by Bacille Calmette-Guérin vaccination) (NDoH, 2014).

2.6.4. Other adjunctive tests

Adjunctive tests can include chest X-rays, ultrasound, computerised tomography (CAT) and Magnetic Resonance Imaging (MRI), the erythrocyte sedimentation rate (ESR) test and Adenosine DeAminase (ADA) detection.

Chest X-rays, despite that they can result in the over-diagnosis of TB, can also miss the diagnosis of TB, as many other diseases mimic TB on an X-ray. Chest X-rays are necessary

for patients who cannot produce sputum or who have negative Xpert results and are HIV positive, and where extra-pulmonary TB (such as pleural effusions and pericardial TB) is suspected (NDoH, 2014; van Cleeff, Kiviha-Ndugga, Meme, Odhiambo & Klatser, 2005). Additionally, ultrasound are used as a supplementary test in the diagnosis of extrapulmonary TB (NDoH, 2014). Computerized Tomography and Magnetic Resonance Imaging are extremely expensive, but they can prove useful for imaging TB lesions which may not be visible on a standard X-ray (NDoH, 2014). While Erythrocyte Sedimentation Rate (ESR) test is not a confirmatory test for TB, but is a complimentary test, as a number of other infections and diseases also result in elevated ESR (NDoH, 2014; Al-Marri & Kirkpatrick, 2000) Lastly, ADA is an enzyme found in most cells, but it becomes elevated in TB effusions (>30µl) (NDoH, 2014).

Despite all the above measures to diagnose TB, traditionally TB services have relied on passive, self-presentation of persons with TB symptoms to the health facilities (NDoH, 2014). However, due to the increase of DR-TB, it is crucial to increase the awareness of TB and DR-TB to ensure the early identification of TB, via the appropriate and available testing methods, which can assist in the prevention or reduction of the transmission of TB (NDoH, 2014).

2.7. Treatment of Tuberculosis

As a result of the variety of risk factors that expose people to the higher possibility of contracting TB, treatment of the infected individual is thus not only essential for the patient, but also for the individuals in his/her environment. If the infection goes untreated, each person with active TB disease will infect on average between ten and fifteen people every

year, as the disease is airborne (WHO, 2012). All types of drug-susceptible TB (pulmonary and extra-pulmonary) are treated in the same way (NDoH, 2014). However, DR-TB requires treatment with different drugs and a different regimen.

2.7.1. History

The South African National TB Association, established in 1947, describes the history of TB in South Africa. The knowledge of the history of TB in South Africa is relatively limited, due to the lack of data during the apartheid era.

The significant changes to TB control started in 1994 when South Africa recruited expert external help for the first time with a visit by Dr Karel Styblo, ex-director of scientific activities at IUATLD, to perform a rapid appraisal of the TB situation. Dr Styblo found that the national guiding principle (established in 1979) was not instigated, there was a lack of focus on infectious cases (smear positive), and the information system was insufficient (SANTA, 2013).

In 1995, a revised National TB Control Program (NTCP) was established based on the WHO's Directly Observed Short Course. The programs aim was the application to gradually replace the non-standardized of short -course chemotherapy in use throughout the country for several years (SANTA, 2013). In 1996, South Africa requested the assistance of the WHO to evaluate the epidemiology and control activities of TB in order to produce a recommendation to improve TB control and treatment in South Africa (SANTA, 2013).

In 2012, the South African government produced a National Strategic Plan (NSP) for tacking HIV, Sexually Transmitted Disease and TB. The plan aimed to control the spread of TB with the ambitious aim of zero new TB infections and deaths by 2032, and a halving of the 2012 rates by 2016 (Knight et al., 2015).

2.7.2. Drug-Susceptible Tuberculosis

Effective TB drug treatments were first developed in the 1940s. In South Africa, the recommended treatment for new cases of drug-susceptible TB complies with international guidelines (NDOH, 2014). The standard six-month treatment regimen of four first-line drugs consists of an intensive phase lasting two months and a continuation phase lasting four months (NDoH, 2014). The TB drugs used are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol/Streptomycin. Standardised regimens use a combination of medicines, and fixed-dose combination tablets are also available for adults and children in some cases. Pyridoxine (Vitamin B6), as an adjunctive treatment, is implemented for all adults and corticosteroids is recommended in extra-pulmonary TB cases (NDoH, 2014).

The drugs can also result in side effects as in Table 2.1.

Table 2.1

Side Effects Associated with TB medication

Drug	Side Effects
Rifampicin	Anorexia, nausea and abdominal pains
	Orange/red coloured urine
	Skin rash
	Jaundice
	Vomiting
	Confusion
	Generalised purpura
Isoniazid	Burning sensation in the feet
	Skin rash
	Jaundice
	Vomiting
	Confusion
Pyrazinamide	Jaundice
	Vomiting
	Confusion
Streptomycin	Skin rash
	Deafness
	Dizziness
Ethambutol	Visual impairments

(NDoH, 2014)

Globally, in 2013 the treatment success rate was 86% among all new TB cases (WHO, 2015). In 2012, the treatment success rate TB patients in relation to HIV was persistently worse for HIV-positive TB patients (74%) than HIV-negative TB patients (88%).The difference was smaller in the African region (75% and 83%, respectively). Conversely, there were substantial differences in the Western Pacific and Eastern Mediterranean Regions, where the treatment success rates among HIV-positive TB patients were only 55% and 53% respectively, compared with 94% and 82% among HIV-negative patients (WHO, 2014a).

2.7.3. Drug-Resistant Tuberculosis – Internationally

The 2016 WHO guidelines for the treatment for DR-TB are a revision of the 2011 guidelines. In an article by Pontali et al. (2013), a study in MDR-TB patients showed that the use of amikacin, kanamycin, capreomycin, moxifloxacin, ethionamide/prothionamide, and cycloserine were all correlated with considerably higher probabilities of treatment success (Pontali et al., 2013). These 2011 guidelines were amended slightly in 2016 specifically with regard to the classes of drugs, duration of treatment and the role of surgery.

Ahuja et al. (2012) conducted a patient meta-analysis to assess the impact on outcomes of the type, number, and duration of drugs used to treat MDR-TB. This analysis was based on the retrospective analysis of 9153 patient records from individuals with resistance to at least isoniazid and rifampicin, from 32 observational reviews investigating the effect of type, number of drugs and cycle of treatment on the outcome (Ahuja et al., 2012). From this examination, the general treatment success in this group was 54%. The study showed that the probability of treatment success is uppermost using at least four in-vitro susceptible drugs in the intensive phase of treatment and at least three susceptible drugs during the continuation phase for patients who had not received second-line drugs beforehand. The study also emphasised the importance of later-generation fluoroquinolones

for effective treatment and the possible benefit of ethionamide and prothionamide in DR-TB. The most significant chance for positive treatment outcomes was with an intensive phase (including an injectable in the) for seven to eight and a half months, and a total treatment duration of 25–27 months. This study underlines the massive challenges of DR-TB treatment. These guidelines DR-TB for management are based on retrospective, observational data, where just half of the patients successfully completed treatment (Ahuja et al., 2012).

2.7.3.1. Drugs.

Treatment for DR-TB (both RR-TB and MDR-TB) involves the inclusion of four categories or groups (A to D) of drugs. In patients with DR-TB, a regimen with at least five effective TB drugs during the intensive phase is recommended, including pyrazinamide and four core second-line TB medications - one chosen from group A, one from group B, and at least two from group C2 (Table 2.2). If this regimen cannot be given for some reason, an agent from group D2 and other agents from D3 may be added to bring the total to five effective TB regimens.

Table 2.2

WHO recommended medication for the treatment of RR-TB and MDR-TB (WHO, 2016b)[1]

	Category of Medication		Name of Medication	Abbreviation of Medication
A.	Fluoroquinolones[2]		Levofloxacin	Lfx
			Moxifloxacin	Mfx
			Gatifloxacin	Gfx
B.	Second-line injectable agents		Amikacin	Am
			Capreomycin	Cm
			Kanamycin	Km
			(Streptomycin)[3]	(S)
C.	Other core second-line agents[2]		Ethionamide/Prothionamide	Am
			Cycloserine/ Terizidone	Cm
			Linezolid	Km
			Clofazimine	(S)
D.	Add-on agents (not part of the core MDR-TB regimen	D1	Pyrazinamide	Z
			Ethambutol	E
			High-dose isoniazid	H^h
		D2	Bedaquiline	Bdq
			Delamanid	Dlm
		D3	*p*-aminosalicylic acid	PAS
			Imipenem-cilastatin[4]	Ipm
			Meropenem[4]	Mpm
			Amoxicillin-clavulanate[4]	Amx-Clv
			(Thioacetazone)[5]	(T)

Note. [1]The intention of this regrouping is to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised (See Section A);
[2]Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations);
[3]In some cases, streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of XDR-TB;
[4]Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin
[5]HIV-status must be tested and confirmed to be negative before thioacetazone is started.

Class B consists of the aminoglycosides, which are bactericidal aminoglycosidic aminocyclitols. They are used for the treatment of TB but also used for advanced bacterial infections (Schacht, 1993). Aminoglycosides investigated explicitly in the current study, kanamycin, as well as polypeptides, specifically capreomycin, have been shown to be toxic; both ototoxic and nephrotoxic (Njuguna, 2013). Nephrotoxicity results from acute tubular necrosis as these drugs appear to concentrate in the renal tubular cell (Alamadi & Rutka, n.d). Ototoxicity, a significant public health concern is occurring in the DR-TB population, specifically in South Africa (Njuguna, 2013).

In the industrialised world, aminoglycosides are limited generally to treat severe infections, due to their toxicity. In the developing world, such as South Africa, aminoglycosides are used more frequently because of their low-cost potent antibacterial activities, outrivalling more expensive antibiotics with less severe side effects (Huth et al., 2011). Despite their toxicity, they are still in the WHO (2016b) guidelines for the treatment of DR-TB.

The WHO does not recommend alternate and more recent drugs such as bedaquiline and delamanid for routine use in MDR-TB treatment. However, they remain as options in cases where acceptable schedules are impossible to design with medications from the other groups (WHO, 2014b). In South Africa, they are referred to as third-line-drugs and are currently only available at designated sites and are only available to patients with specific criteria (NDoH, 2015).

Further, for the HIV positive population, along with the complicated DR-TB medication regimen, the inclusion of antiretroviral therapy (ARV) is a necessary factor in the HIV infected patients' treatment. ARV is advocated for all patients with HIV and DR-TB needing second-line anti-tuberculosis drugs, irrespective of CD4 count, promptly (within the first eight weeks) following initiation of TB treatment (WHO, 2011).

2.7.3.2. Duration.

Currently, in the treatment of patients with DR-TB, the WHO suggests an intensive phase of eight months for most patients, and modifications to the duration may ensue according to the patient's response to therapy (conditional recommendation, very low-quality indication) with a total treatment duration of 20 months (WHO, 2014b).

According to the WHO, where a shorter duration is based on a qualified recommendation with very low-quality evidence, the updated guidelines in 2016 include a shorter duration. They include patients with RR-TB or MDR-TB who have not previously received treatment with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered implausible. For these patients, a shorter MDR-TB regimen of nine to 12 months may be utilised instead of a conventional regimen (WHO, 2016b).

The optimal duration for treatment of patients with DR-TB, however, differs between individuals as it depends on a variety of factors, such as the extent of the disease, the immune status of the patient, and the virulence and the drug resistance of the causative strain of *M. tuberculosis*. Personalization of the duration of treatment for DR-TB would be highly beneficial. Until recently there has been little interest in the identification of biosignatures that could eventually lead to individual recommendations for the duration of anti-TB therapy (Heychendorf et al., 2014).

2.7.3.3. Surgery.

In patients with RR-TB and MDR-TB, elective partial lung resection (lobectomy or wedge resection) may transpire alongside a recommended MDR-TB regimen (WHO, 2016b).

2.7.4. Drug-Resistant Tuberculosis: South Africa

2.7.4.1. Regimen.

In South Africa, all patients newly diagnosed with DR-TB (MDR-TB and RR-TB) receive a standardised treatment regimen, unless otherwise indicated. Four weight bands guide the administration of the medication: <33kg, 33-50kg, 50-70kg and > 70kg. The dose of the injectable is provided respectively at: 15-20 mg/kg, 500-750 mg/kg, 1000 mg/kg and 1000/kg mg respectively (NDoH, 2011). This regimen complies with the international standards specified by the WHO (2011) and since 2014 includes delamanid and bedaquiline. Depending on prior use and tolerability, different drugs are utilised. However, mostly, treatment involves a standardised regimen which consists of at least six months intensive phase treatment with five drugs: moxifloxacin, ethionamide, terizidone, pyrazinamide and an injectable (kanamycin/amikacin) taken at least six times per week during the injectable phase. A continuation phase treatment ensues with four drugs; moxifloxacin, ethionamide, terizidone and pyrazinamide taken at least six times per week for 18 to 24 months beyond culture conversion (NDoH, 2011; NDoH, 2015). Isoniazid may be included in the DR-TB regime depending on the patient's resistance profile. Wolff and Nguyen (2012) discussed how the limitation of the use of ethionamide is because of the low therapeutic index and high risk of toxicities. Two research groups reported the identification of ethionamide potentiators that significantly sensitise *M. tuberculosis* to the drug through the inactivation of a key resistance mechanism (Wolff & Nguyen, 2012).

The NDoH (2011) mentions that kanamycin and amikacin are parenteral drugs that are structurally similar. Strains of TB that are resistant to streptomycin are usually susceptible to kanamycin and amikacin. When a patient is resistant to kanamycin, the kanamycin often induces almost complete cross-resistance with amikacin, and thus they should be considered as the same drug. Amikacin is as active as kanamycin and better tolerated, but is much more

expensive, and thus kanamycin is more frequently used (Rossiter et al., 2012). Capreomycin can be considered as the injectable in place of kanamycin and amikacin for patients with hearing loss, as it is less toxic. It is also more expensive, and not as readily available. Culture conversion guides the duration of the injectable phase which occurs when a patient obtains two consecutive negative TB cultures (30 days apart). The injectable phase is determined by adding four months to the culture conversion date if the total duration is less than six months and then adding 18 months to the culture conversion date without the injectables.

Recently, third line drugs have been introduced for the management of DR-TB, and includes bedaquiline, delaminid, andlinezolid, however, these medications are currently only available at designated sites and are only available to patients with specific criteria. Third-line drugs would replace the injectable, yet have strict eligibility criteria, such as XDR and pre-XDR, MDR with inhA and katG mutations both present, any RR-TB patient (MDR or rifampicin mono resistant) who develops treatment-related toxicity (hearing loss, renal failure, psychosis, etc.) and any rifampicin resistant patient who has pre-existing hearing loss or renal failure (NDoH, 2015). bedaquiline, delaminid, and dinezolid are not yet widely available, and so toxicity is still occurring. However, linezolid in managing XDR-TB has also shown limitations due to its high cost as well as other toxicity (myelosuppression and neuropathy), which appears to be determined by dose (>600 mg daily) and duration (Pontali et al., 2013). Studies have shown delamanid is one of the most promising compounds; it demonstrated an increase in the sputum-culture conversion rate at two months in patients with MDR-TB, when used in combination with a background regimen developed according to the WHO guidelines (Pontali et al., 2013). Capreomycin is considered a third-line drug as well in the new South African Department of Health Guidelines (2015). In practice, when patients are receiving their treatment as outpatients, they only receive their injectable five days a week, instead of the above stated ‘at least six times’ a week.

Despite these new drugs, a paediatric study showed that more than 90% of children receive successful treatment and a non-severe disease could be treated with reduced treatment duration. Reduced treatments duration is however generally for children younger than eight years, as they metabolise drugs differently. There is no regimen though specifically for children (less than eight years); only according to weight bands (Seddon, Hesseling, Godfrey-Faussett & Schaaf, 2015). This shows the necessity to possibly 'fine-tune' the dosing regimen based on various factors, other than weight, and the possibility of incorporating the existing, less expensive drugs, with a change in administration and/or dosage, possibly guided by pharmacokinetics.

2.7.4.2. Decentralisation.

Prior to the implementation of the new guidelines, TB treatment in South Africa was centralised (NDoH, 2011). It involved the hospitalisation of patients from diagnosis with DR-TB (RR-TB and MDR-TB) and XDR-TB until they received two negative TB cultures taken 30 days apart. Thus, patients were hospitalised for months, and there were long waiting lists for patients needing admission to these centralised DR-TB treatment units. This centralised treatment resulted in a delay in the initiation of treatment in some provinces of up to three or four months. Of approximately 9070 cases of MDR-TB notified in 2009, fewer than 5000 started treatment in the nine provinces. In 2010, there was a higher percentage of those diagnosed with MDR-TB starting treatment; however, there was still a significant gap (71% in 2010 in comparison to less than 55% in 2009). Thus, several patients could die before starting treatment. The number of patients diagnosed with MDR-TB far exceeded the number of hospital beds in the centralised MDR-TB units. The waiting times and waiting lists also resulted in many infectious and untreated patients exposing family and community members to DR-TB bacilli (NDoH, 2011).

Furthermore, nosocomial transmission of MDR/XDR-TB occurs in health facilities when infection control measures are not adequately implemented as there is substantial evidence that more than half of all XDR-TB infections are acquired in hospitals (NDoH, 2011). Patients also refused hospitalisation, and post hospitalisation, the monthly follow-ups were lengthy and unpleasant, which contributed to poor outcomes (NDoH, 2011).

From other studies, full inpatient treatment or centralisation is also costly. A study by Sinanovic, Ramma, Vassall et al. (2015) investigated the costs of inpatient treatment in South Africa. They found that a fully hospitalised model was 42% more costly than the fully decentralised model (US $13 432 versus US $7 753 per patient). The annual total cost of treating all diagnosed cases ranged from US $110 million in the fully decentralised model to US $190 million in the fully hospitalised model. This cost of inpatient treatment may be unaffordable for a developing country such as South Africa. Based on this unfeasible option of hospitalisation, the NDoH proposed the decentralisation of treatment of patients with MDR-TB (not XDR-TB).

The rationale for decentralisation was that it would shorten the number of days between diagnosis and treatment, increase treatment coverage, reduce the transmission by initiating treatment sooner, make it possible for patients to receive treatment in their homes and increase the social acceptance of treatment (NDoH, 2011). It would improve cost-effectiveness by reducing lengthy hospital stays in specialised hospitals. This model mentions that each province should still have a specialised MDR/XDR-TB unit, yet additional DR-TB decentralised units with the establishment of several satellite units. These guidelines mention a study by Nardell and Churchyard (2011) who describe the long-standing evidence suggesting that TB patients on effective therapy rapidly become non-infectious and that unsuspected, untreated TB cases account for most transmission.

Despite the positive aspects of decentralisation, areas of concern have been identified with this model. A community-based DR-TB treatment program in Khayelitsha, South Africa was investigated (Moyo et al., 2015). Moyo et al. (2015) investigated loss from treatment (LFT), and post-treatment outcomes of DR-TB patients in this setting. Loss from treatment was defined as an interruption of treatment for ≥2 consecutive months, and it was assessed among patients initiating DR-TB treatment for the first time. Patients were traced through conventional data sources to identify those who subsequently restarted treatment and those who died. Community DR-TB counsellors and provided additional information on patient status and survival as well as the use of the national death registry. Among 452 patients initiating treatment for the first time within the given period, 30% were LFT, with 67% retention at 18 months. Treatment was restarted in 20% of the patients, with additional resistance recorded in 8%, excluding two with presumed DR-TB. Overall, 25% of the patients died. In summary, LFT was high, occurred throughout the treatment period and was unusually high among males and those aged 15-25 years. Overall long-term survival was poor. Community-based treatment is not merely an alternative to centralised treatment, and the decentralisation model needs to address these issues (Moyo et al., 2015).

In order to compromise and find a fair 'medium', Padayatchi and Friedland (2008) proposed an intermediate suggestion, between centralisation and decentralisation. They suggested the admission to institutions of patients with MDR-TB or XDR-TB closer to their homes with subsequent discharge and home-based care. Intermediate – between centralization and decentralisation could perhaps alleviate the transmission of the infection to others as they would be hospitalised in the infectious stage. However, infection control within DR-TB hospitals within South Africa has been shown to be poor, which is also a concern of inpatient treatment, whether long- or short-term (Farley et al., 2012). Although this

decentralisation model is based on valid facts, decentralisation is not the simple solution, and perhaps this medium or a partially centralised system needs further investigation.

2.7.5. Factors that influence treatment outcomes

Treatment outcomes, despite the regimens available, appear to be mediocre, and often unavailable. Globally in 2012, a mere 17% of total estimated cases of MDR-TB started treatment (Günther, 2014). Of the cohort of patients with MDR-TB who started treatment in 2010, only 48% had a successful treatment outcome, reflecting high rates of either loss to follow up and/or mortality. In 2012, 78,000 MDR-TB cases were estimated in the European region, as defined by the WHO, yet only approximately 30,000 patients were detected, and even fewer started treatment (Günther, 2014). Falzon et al. (2013) reported a successful treatment outcome for 64% of patients with MDR-TB, yet only 40% of patients with XDR-TB.

Similarly, in an article by Gajee et al. (2016), in 2014, South Africa initiated 11 538 patients with RR-TB, including MDR-TB, on second-line TB treatment. Of the 2012 cohort of RR-TB cases, only 52% had a reported treatment outcome, with no reports on the remainder. Among the patients with outcomes, the RR-TB treatment success rate was 49% (Gajee et al., 2016). This unavailability of data or LTF is an important factor with regards to the feasibility of research.

Whether treatment is centralised, decentralised or partially centralised, other factors may also affect treatment outcomes and needs to be addressed. HIV has shown to have significant influence on the treatment outcomes. Adherence to treatment, particularly with decentralisation has also become a factor affecting outcomes.

2.7.5.1. Influence on HIV on TB treatment and outcomes.

A particularly prevalent factor within the TB population includes HIV (Narasimhan et al., 2013). HIV coinfection exacerbates the severity of TB disease while additionally, TB

coinfection accelerates HIV replication in affected organs including lungs and pleura (Narasimhan et al., 2013). In 2007 nearly 20% of South Africa's adult population was infected with HIV, making South Africa home to one of the world's worst HIV epidemics, and one of the highest TB burdens (Andrews, Shah, Gandi, Moll & Friedland, 2007). These two diseases, HIV and TB, are seemingly related. In an article published in 2010 by Getahun, Gunneberg, Granich and Nunn, it described how of the 33.2 million individuals infected with HIV, one-third are projected also to be infected with TB. This article mentioned in 2008, that there were an estimated 1.4 million new cases of TB among persons with HIV infection, and TB accounted for 26% of AIDS-related deaths. The relative risk of TB among HIV-infected persons, compared with that among HIV-uninfected persons, ranges from 20- and 37-fold, depending on the state of the HIV epidemic (Getahun et al., 2010).

Also, diagnosis of TB and DR-TB is challenging in the presence of HIV disease, and HIV-infected individuals undergoing treatment for MDR-TB have lower rates of treatment success and higher mortality rates than do HIV-uninfected patients (Andrews et al., 2007). The treatment success rate for HIV-uninfected patients in South Africa was 53%, contrasted with 38% for HIV infected patients. Andrews et al. (2007) further mentions that HIV clinics are sites are clustering of TB susceptible individuals, and, in the presence of unrecognised TB, they provide another favourable setting for the rapid spread of DR-TB (Andrews et al., 2007).

In 2012 about 320 000 people died of HIV-associated TB. Also, almost 25% of deaths among people with HIV are due to TB. In 2012, there were an estimated 1.1 million new cases of HIV-positive new TB cases, 75% of whom were living in Africa (WHO, 2013). Due to the devastating effect of HIV on susceptibility to TB, sub-Saharan Africa has been affected disproportionately and accounts for four of every five cases of HIV-associated TB (Lawn & Zumla, 2011).

Furthermore, Gandhi et al. (2010) conducted a study in Tugela Ferry, South Africa regarding DR-TB outcomes with the DR-TB population. They illustrate that from 2005 to 2007, 272 MDR-TB and 382 XDR-TB cases were diagnosed, while the HIV coinfection rates were 90-98% respectively. Also, mortality within a year was 71% for MDR-TB and 83% for XDR-TB patients with 40% of MDR-TB and 51% of XDR-TB cases dying within 30 days of sputum collection. In contrast, patients with MDR-TB and XDR-TB have achieved treatment success rates of 60 to 80% and 44 to 60%, respectively, in low HIV–prevalence settings (Gandhi et al., 2010).

2.7.5.2. Treatment adherence.

Adherence is described as the extent to which patients follow the instructions they are given for prescribed treatments (Munro, Lewin, Smith, Engel, Fretheim & Volmink, 2007).

Gajee et al. (2016) discuss the concern of missing appointments and adherence to treatment with the implementation of outpatient decentralised RR-TB treatment in South Africa since late 2011. These missed appointments can also lead to treatment interruptions contributing to the constant amplification of resistance, ongoing transmission of RR-TB, and an increased risk of morbidity and mortality. They found at an outpatient clinic, at Helen Joseph Hospital, more than half the patients missed at least one appointment which occurred within the first three months after treatment initiation and 39.5% missed three or more (Gajee et al., 2016).

Other variables can further influence the adherence, within this outpatient treatment regimen. These factors are multifactorial and can include social factors such as poverty, education, support systems, stigma, emotional influences such as depression, coping skills; as well as the perception about TB and treatment.

To illustrate these factors, a study done in Zambia looked at drug adherence for TB (not DR-TB) in a community-based intervention. This study found that 29.8% of the patients

stopped taking their medication while age, marital status, and educational levels were not significantly associated with compliance. The primary factors leading to noncompliance included patients beginning to feel better, inadequate knowledge on the benefits of completing a course, running out of drugs at home and the adverse effects (Kaona, Tuba, Siziya & Sikaona, 2014). Adherence was further investigated in a hypertension study (Morisky, Ang, Krousel-Wood & Ward, 2008); which can be applied to patients with TB or DR-TB. This study noted that adherence to the medication was affected negatively by depression, lack of knowledge about hypertension, the complexity of the medication regimen, health care system perceptions by the patient, sexual dysfunction, side effects of medication, and reduced quality of life. This study found that awareness of hypertension, patient fulfilment, and coping skills was significantly associated with medication adherence (Morisky et al., 2008). Three themes emerged in another study with regards to loss to follow-up, namely: struggle with prolonged treatment, strive against stigma and toward support and divergent perceptions and practices. Daily injections, pill burden, DOT, migratory work, social problems, prior TB treatment, and adverse drugs effects were reported as significant barriers to treatment adherence and retention-in-care by patients and providers. This study also reported the influence of traditional healers (Shringarpure et al., 2016).

Additionally, level of education, age, and social support can influence this adherence. A study by Hutapea (2009) in Indonesia looked at factors affecting compliance to medication in TB (not DR-TB). He found that the higher the education, the greater the age and the more family support indicated better adherence to medication.

Poverty is a significant influence on adherence. A study conducted in Uganda looked at non-adherence to TB drugs among TB/HIV co-infected patients (Amuha, Kutyabami, Kitutu, Odoi-Adome & Kalyamgo, 2009). One of the findings in this study for non-adherence was a lack of transport money to collect more drugs when they were finished as well as being

busy at work (Amuha et al., 2009). This issue, such as lack of transport money needs addressing to improve retention in patient care (Gajee et al., 2016).

Addressing some of the issues with adherence could improve retention. The implementation of a psychosocial support program showed success in reducing default among MDR-TB patients (Kaliakbarova et al. 2013). Based on the factors mentioned affecting adherence, this could be a measure to assist in retaining patients in the treatment programs.

An issue, looking beyond social and emotional factors of patients, looked at discrepancies between what doctors prescribe and what patients take in actual practice, regardless of disease or illness (Bedell, et al., 2000). This study showed discrepancies in outpatient treatment among 76% of the sample. Although this study did not explicitly address HIV and TB medication, it can be extrapolated to this population (Bedell et al., 2000).

As adherence is an issue, new drugs need development, or the treatment needs refining. The extension of the TB regimen often causes side effects. Therefore, for the first time in four decades, new TB drugs are developing, and many are currently in clinical trials. There are also several TB vaccines in Phase I or Phase II trials (WHO, 2014a). Not only is active TB management critical, but latent TB management is a new component of the WHO new post-2015 End TB Strategy (WHO, 2015).

Non-adherence to treatment remains a significant obstacle to effective TB and DR-TB control in developing countries. Additionally, the dual infection of TB and HIV presents further adherence problems because of high pill burden and adverse effects (Amuha et al., 2009). These adherence factors affect the feasibility of the implementation of studies in this population that are specifically drug related.

Chapter 3: Pharmacology of Kanamycin and Capreomycin

This chapter introduces pharmacology to include pharmacokinetics, pharmacodynamics, and pharmacotherapeutics. Pharmacokinetics is further introduced and includes routes of drug administration, absorption, distribution, metabolism, and elimination of drugs. Pharmacodynamics in then briefly introduced. The concept of design and optimisation of a dosage regimen is presented followed by aminoglycoside pharmacokinetics and optimisation of the regimen. The chapter concludes by describing the pharmacokinetics of kanamycin and capreomycin which are utilised to treat patients with DR-TB.

3.1. Pharmacology

Pharmacology is the study of all aspects of drugs (Brucker & King, 2011). Pharmacotherapeutics, a further branch of pharmacology, is defined as "the study of the therapeutic uses and effects of drugs" (Merriam-Webster, 2018) or in other words the study of beneficial and adverse effects of drugs, concentrating on the treatments' effect of drugs (Brucker & King, 2011). Various terms are used to explain the scope in this field of study, such as pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the absorption, distribution, metabolism, and excretion of drugs (Brucker & King, 2011).

3.2. Pharmacokinetics

Pharmacokinetics refers to what the body does to the drug. It includes factors namely absorption, distribution, metabolism and elimination (Brucker & King, 2011; Clark et al., 2012). These pharmacokinetic factors determine the amount of the drug at the target sites for

action. Pharmacokinetic considerations allow the clinician to develop and optimise treatment regimens (Clark et al., 2012). These decisions include amongst other the route of administration for the specific drug, the amount and frequency of each dosage and the length of treatment (Clark et al., 2012; Cianfrone et al., 2011).

3.2.1. Routes of drug administration

The administration of drugs transpires through several routes namely topical, enteral and/ or parenteral (Satoskar, Bhandarkar, & Rege, 2009). Enteral administration, the most commonly used route for administration of drugs, includes oral and sublingual administration. Enteral administration is the safest, often particularly accessible and is a very cost-effective method of drug dispensation. Parenteral administration includes intravenous (IV), intramuscular (IM) and subcutaneous (SC). The dispensation of a drug's route is determined by the drug properties, as well as the therapeutic objectives (Clark et al., 2012). DR-TB drugs are administered both enterally and parentally; the regimen consists of both oral drugs and the injectable which is administered intramuscularly.

Oral drug preparations include enteric-coated and extended release medication. Oral drugs have a low risk of systemic infections compared to parenteral administration, but many factors affect the route of administration. The pathways in oral absorption are the highly complex and the low pH of the stomach can disable some drugs (Clark et al., 2012). The standardised DR-TB regimen includes two phases; phase one which is the intensive/injectable phase where a combination of injectable and oral drugs is provided. Phase two is the continuation phase where only oral drugs are used. The DR-TB regimen includes five oral drugs throughout treatment (NDoH, 2013). Yet, disadvantages of this oral administration can include the limited absorption of some drugs, patients' compliance is necessary, and food may affect absorption (Clark et al., 2012).

Sublingual route of administration, although also enteral, is not included in the DR-TB regimen. It includes placement of the drug under the tongue to allow the drug to distribute into the capillary network and therefore enter the systemic circulation promptly (Clark et al., 2012).

While enteral involves oral administration, parenteral administration introduces a drug directly across the barrier defences into the systemic circulation (Clark et al., 2012). This parenteral route of administration in the DR-TB regimen is also used. These parenteral routes are used for drugs that are inadequately absorbed and unstable in the gastro-intestinal (GI) tract as they have the highest bioavailability and are not sovereign to first-pass metabolism or severe GI environments. It allows a rapid effect and a concentrated measure of control over the spreading levels of the drug as absorption is not required.

The aminoglycoside compound, such as kanamycin for DR-TB, consists of an aminocyclitol moiety with two or more amino sugar rings. Aminoglycosides are polycationic (positive charge) and are highly polar, this means that enteral absorption is reduced, and aminoglycosides are administered generally parenterally or topically (Huth et al., 2011). The parenteral method for DR-TB drugs is mostly IM injections, such as for kanamycin, capreomycin, amikacin or viomycin (NDoH, 2013). Intramuscular drugs can be administered in aqueous solutions which are absorbed rapidly or in specialised depot arrangements which are absorbed slowly. As the medium circulates out of the muscle, the drug precipitates at the site of the injection. The drug then dissolves gradually, providing a constant dose over a protracted period (Clark et al., 2012).

Intravenous is the most common parenteral route for drugs that cannot be absorbed orally, but it is not used typically in the DR-TB regimen. Intravenous drugs can be administered via an injection or an IV infusion over a more extended period. Intravenous

infusion allows for a reduction in the uttermost plasma concentration and an enhancement of the time of the drug in the system (Clark et al., 2012).

Subcutaneous administration, like IM, requires absorption via simple diffusion and is slower than the IV route. SC minimises the risks of haemolysis or thrombosis accompanied with IV injection and may provide constant, slow and lasting effects (Clark et al., 2012).

Other routes of administration can include oral and nasal inhalation, intrathecal/intraventricular, transdermal, rectal and topical (Clark et al., 2012; Satoskar et al., 2009).

3.2.2. Pharmacokinetic Parameters

After administration of the TB drugs, via the enteral or parenteral route, further movement of the drug through and out of the body is determined by the four pharmacokinetic parameters, namely absorption, distribution, metabolism, and elimination.

3.2.2.1. Absorption of drugs.

Absorption of a drug refers to the transfer of the drug from the site of administration to the bloodstream (Clark et al., 2012; Atkinson et al., 2012). The drug absorption from the site of administration allows the entry of the therapeutic agent into the plasma. The rate and efficacy of the absorption depend on intrinsic and extrinsic factors medication (Martinez, Gordon & Amidon, 2002).

Intrinsic factors are described as patient attributes that can affect drug absorption, such as the integrity of the gastrointestinal tract, physiological status, site of drug absorption, membrane transporters and pre-systemic drug metabolism medication (Martinez, Gordon & Amidon, 2002). Furthermore, the blood flow to the absorption site also has an effect; as the intestines have a much better blood flow than the stomach, incorporation from the intestine is preferred to absorption from the stomach (Peck et al., 2014). When a drug moves extremely fast through the GI tract, for example in cases of diarrhoea, absorption will be reduced,

demonstrating how the contact time at the absorption surface has an effect of the absorption (Clark et al., 2012).

Extrinsic variables, unlike patient attributes, involve aspects such as the effects of food or other concomitant medication (Martinez, Gordon & Amidon, 2002). With the DR-TB population, there may be other concomitant medication, such as ARV. Furthermore, extrinsic factors, such as malnutrition (Williams, Davis & Lowenthal, 1993), may also be present affecting the absorption. The pH of the drug can affect the absorption, as the drug will pass through membrane more readily if it is uncharged (Peck et al., 2014). Likewise, the expression of P-glycoprotein will have an effect. P-glycoprotein is a multidrug transmembrane courier protein in charge of transporting various molecules, as well as medications, across the cell membrane. Thus, in areas of high presence, P-glycoprotein diminishes drug absorption, as it transfers many drugs out of the cells. It is also correlated with multidrug resistance (Mahar, Doan et al., 2002; Clark et al., 2012).

These extrinsic factors influence the drugs' bioavailability, defined as the fraction of the drug that reaches the systemic circulation (Clark et al., 2012). For IV administration, absorption is complete, and 100% bioavailability is achieved (Clark et al., 2012). Drug distribution by other routes may result in less incorporation, and less bioavailability (Clark et al., 2012), such as oral administration of some of the DR-TB drugs.

With aminoglycosides, after parenteral administration, plasma levels peak between 30 to 90 minutes (Huth et al., 2011). The absorption of capreomycin, the polypeptide, is expected and achieves a peak serum concentration in one to two hours after administration (Black, Griffith & Peabody, 1966).

Dependant on drug properties; the drugs are absorbed from the gastrointestinal tract by either passive diffusion, facilitated diffusion, active transport or endocytosis (Clark et al., 2012). The majority of drugs are absorbed by passive diffusion where drugs move from a

region of high concentration to low concentration (Di et al., 2012; Le, 2016). Facilitated diffusion occurs when agents enter the cell through dedicated transmembrane carrier proteins that facilitate the movement of sizeable molecules, while active transport also includes exclusive carrier proteins that traverse the membrane (Peck, Hill & Williams, 2014). Lastly, endocytosis and exocytosis involve drug delivery whereby the drugs are exceptionally large (Clark et al., 2012).

When discussing absorption, the consideration of bioavailability is vital. Determining the bioavailability is essential when calculating drug dosages. The route of administration and the chemical properties of the drug will affect bioavailability (Atkinson et al., 2012).

3.2.2.2. Distribution of drugs.

Distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium and intracellular fluids (Clark et al., 2012). Four main factors are considered in the distribution of drugs namely; blood flow, capillary permeability, the amount of uniting of the drug to the plasma and tissue proteins and the volume of distribution (Clark et al., 2012).

The rate of blood flow can affect the distribution (Galvin, Drummond & Nirmalan, 2007). The rate of blood flow to the tissue capillaries varies widely between individuals because of the unequal circulation of cardiac production to the various organs. For example, blood flow to the brain, liver, lungs, and kidneys is higher than to the skeletal muscles. This is relevant as DR-TB occurs in the lungs. Adipose tissue, skin, and viscera have lower rates of blood flow, while high blood flow is seen in the central nervous system, as this high blood flow and high lipid solubility produces anaesthesia (Clark et al., 2012).

Capillary permeability, another factor affecting distribution, refers to the capacity of the capillary to allow the flow of the drugs in and out of the capillary (Levitt, 2002). This is determined by the capillary composition and by the chemical type of the drug. Capillary

formation varies widely regarding the fraction of the cellar membrane that is exposed by fissure junctions in the endothelial cells (Clark et al., 2012). Aminoglycosides, such as kanamycin, may enter the endolymph from fibrocytes and capillaries in the lateral wall, strial capillaries or from the perilymphatic scalae (Steyger & Karasawa, 2008).

The third factor, the connecting of drugs to plasma proteins and tissues, is described according to three aspects; binding to plasma proteins, binding to tissue proteins and hydrophobicity (Beaumont, Cole, Gibson & Gosset, 2010). Binding to plasma proteins is relatively non-selective regarding the biochemical assembly and takes place at the sites of the proteins to which endogenous composites usually attach. The reversible binding to plasma proteins sequesters drugs on a non-diffusible form and slows their transfer out of the vascular compartment (Clark et al., 2012). While binding to tissue proteins describes drugs that can accrue as a result of binding to lipids, proteins or nucleic acids. Numerous drugs amass in tissues which can lead to elevated concentrations of the drug in tissues than in extracellular fluid and blood (Clark et al., 2012). Hydrophobic drugs can dissolve in the lipid membranes and therefore saturate the entire cell façade. Hydrophilicity contrasts with hydrophilic drugs, such as aminoglycosides, which do not readily penetrate the cell membranes. The chemical make-up of a drug compellingly shapes its ability to cross cell membranes (Clark et al., 2012; Gulyaeva et al., 2003).

Lastly, the volume of distribution can be described as the fluid quantity that is compelled to hold the whole drug in the body at the same concentration in the measured plasma. This is useful to compare the dissemination of the drug to the quantities of the water sections in the body (Clark et al., 2012; Atkinson et al., 2012; Beaumont et al., 2010).

Once a drug enters a body, it has the capability to spread into any one of the three definite sections of body water or to become segregated into a cellular site. These compartments include the plasma, extracellular fluid and/or total body water. If a drug has a

substantial molecular weight or joins considerably to plasma proteins, it is too sizable to move through the endothelial slit seams of the capillaries and is accordingly confined in the plasma, which makes up about 6% of the body weight. However, if a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions and into the interstitial fluid. However, a drug cannot move across the lipid membrane of the cell to enter the water phase inside the cell. These drugs, therefore, dispense into extracellular fluid (plasma plus interstitial fluid), which makes up about 20% of the body weight. Then, if a drug has a low molecular weight and is hydrophobic, it can move through the plasma and extracellular fluid to the intracellular fluid, which makes up about 60% of the body fluid (Clark et al., 2012; Beaumont et al., 2010).

Many drugs, such as aminoglycosides, distribute into several compartments and often bind cellular components such as lipids, proteins, and nucleic acids. The column into which drugs distribute, to be precise the ‘apparent volume of distribution’ is a valuable pharmacokinetic constraint useful for determining a drug loading dose (Clark et al., 2012).

The drugs’ clearance usually allows the calculation of the volume of distribution, as a perpetual segment of the drug is excreted per unit time. Therefore, it can be analysed by mapping a graph of plasma blood concentration versus time (Benet & Zia-Amirhosseini, 1995, Clark et al., 2012).

A large volume of distribution has an effect of the half-life of a drug because drug elimination depends on the amount of drug delivered to the kidney (or other organs where metabolism occurs) per unit time. Delivery of a drug to the organ of elimination depends on blood flow as well as on the fraction of the drug in the plasma (Clark et al., 2012).

3.2.2.3. Metabolism of drugs.

Metabolism refers to the process where the drug may be bio-transformed by metabolism of the liver, gut wall, lungs, kidney, and plasma or other tissues. The liver, however, is the most common site of metabolism (Schonborn & Gwinnutt, 2010).

Metabolism of drugs, by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerisation, allow the drug's elimination (Le, 2016). When discussing metabolism of drugs, consider the kinetics of metabolism as well the reactions of drug metabolism (Clark et al., 2012).

The kinetics of metabolism consists of zero-order kinetics and first-order kinetics. Zero-order kinetics refers to a drug where a constant amount per unit time is metabolised and the rate does not increase as the drug concentration increases. In contrast, first-order kinetics refers to drugs where a constant fraction per unit time is metabolised, and the rate increases as the drug concentration increases (Clark et al., 2012; Croom, 2012).

The reactions of drug metabolism are an essential factor to consider as the kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents must first be metabolised into more polar (hydrophilic) substances in the liver (Clark et al., 2012).

Drug metabolism for aminoglycosides administered parentally is nominal as approximately 99% of the aminoglycosides are eliminated unaltered by glomerular filtration in the proximal tubule (Huth et al., 2011). As capreomycin is exceptionally similar in organisation to aminoglycosides, it is often compared to and grouped with aminoglycoside antibiotics, such as kanamycin (Reisfeld et al., 2012). Thus, the same would apply regarding the metabolism of capreomycin or kanamycin.

3.2.2.4. Elimination of drugs.

Elimination of drugs from the body requires the drugs to be sufficiently polar for efficient excretion. As the drug enters a system, elimination begins via one or more of the three main routes of elimination namely; (i) hepatic metabolism, (ii) elimination in bile and (iii) elimination in urine. These exclusion processes decrease the strength of a drug in the plasma exponentially. That is, a continuous portion of the drugs' presence is eliminated in a unit of time (Clark et al., 2012; Beaumont et al., 2010).

Elimination or clearance of a drug through the kidney into the urine involves glomerular filtration, proximal tubular excretion and distal tubular reabsorption (Clark et al., 2012; Atkinson et al, 2012). Dissipation via other means include via the intestines, the bile, the lungs, breast milk and others. Aminoglycosides are eliminated unaltered by glomerular filtration in the proximal tubule. The plasma half-life of aminoglycosides ranges from one and a half to three and a half hours but is prolonged in neonates, infants, and conditions with decreased kidney function (Huth et al., 2011).

3.3. Pharmacodynamics

Pharmacodynamics refers to the action of drugs in the body and the influence of drug concentrations on the magnitude of the response (Brucker & King, 2011; Clark et al., 2012). Pharmacodynamics together with pharmacokinetics can help explain the relationship between the dose of the drug and response, in other words, the effect of the drug. This pharmacodynamic response can be affected by a disorder, ageing or other drugs.

Most drugs effects, both beneficial and harmful are through interaction with receptors of the cell surface or within the cell. The drug-receptor complex commences fluctuations in biochemical and/or molecular motion of a cell by signal transduction (Clark et al., 2012).

Other disorders can change receptor binding, alter the level of binding proteins, or decrease receptor sensitivity Ageing can affect pharmacodynamic responses through changes in receptor binding or post-receptor response sensitivity. Furthermore, drug-drug interactions can create competition for receptor binding sites, or they can alter post-receptor responses (Farinde, 2016).

Therefore, in order to maximise a drugs response through TDM, both pharmacokinetics and pharmacodynamics must be considered.

3.4. Therapeutic Drug Monitoring

Therapeutic drug monitoring is the clinical practice of measuring certain drugs at specific intervals to maintain a constant concentration in a patient's bloodstream in order to optimise their dosage regimen (Kang & Lee, 2009). The goal of a drug therapy is to achieve and maintain therapeutic concentration resulting in a therapeutic response while reducing toxic or adverse side effects (Clark et al., 2012). A dosage regimen consists of two main factors; the size of the drug dose and the frequency of drug administration (Shargel, Wu-Pong & Yu, 2012). The dosage and dosage frequency can generally be adjusted if not within this therapeutic range (Clark et al., 2012). To design and optimise the drug regimen, three main areas are considered, namely; continuous-infusion regimens, fixed-dose/fixed-time regimens and optimisation of the dosages (Clark et al., 2012).

Continuous infusion regimens describe some drug therapies that may involve continuous administration of a drug (such as IV) in comparison to a single administration of a drug. The continuous regimens result in the accumulation until stable condition occurs, which is the point at which the amount of drug eliminated equals the amount of drug administered (Clark et al., 2012; Shargel, Wu-Pong & Yu, 2012).

In contrast, a fixed-dose or fixed-time regimen refers to drugs given in fixed doses rather than by continuous infusion as it is often more convenient. Here, fixed-doses and fixed-time periods are dispensed with numerous IV injections or oral administration. Fixed-dose regimens results in time-dependent variabilities in circulating the level of the drug, which contrasts with the soft elevation of drug concentration as with the continuous infusion. With multiple IV injections at regular intervals, the plasma concentration can increase pending the attainment of a steady state. This is the aim of the DR-TB injectables (Clark et al., 2012; Ratain & Plunkett, 2003). The DR-TB regimen involving the injectable aminoglycosides/polypeptides requires the administration of an injection daily when individuals treated as inpatients and injections five days a week when treated as outpatients. (Clark et al., 2012).

Although it is advised in the NDoH guidelines (2015) to reduce the dosage or increase the length of dosing interval when toxicity is observed, the specifics are not explained. From personal communication with medical staff at the two study sites in this current research, the injection is changed often to three days a week when toxicity is noted; however, this is generally after culture conversion. This regimen, however, is at fixed dose/fixed-time intervals to assist in reaching steady state.

Optimisation of the dose is the goal of TDM; to maintain therapeutic efficacy while minimising toxicity and adverse effects. The maintenance of this efficacy by reaching an ideal plasma concentration where therapeutic efficacy is determined. Often, if this plasma concentration is not reached, the prescription and dosage rate can be regulated (Kang & Lee, 2009).

This drug concentration is measured in the plasma with a Liquid Chromatography-Mass Spectrometer (LC-MS). LC-MS/MS is an increasingly vital tool in TDM as it offers improved sensitivity and specificity (Adaway & Keevil, 2012; Grebe & Singh, 2011).

However, the choice of sample preparation method, column technology, internal standard and mass spectrometric conditions is vital to ensure accurate drug measurement and to avoid interference from matrix effects and drug metabolites. This Mass Spectrometry technique is more involved than automated immunoassays, however technological advances such as robots and other automated procedures are being attractive tools and convenient methods to assist in the mass spectrometry technique for therapeutic drug monitoring (Adaway & Keevil, 2012). Mass spectrometry was used in this current study to identify the kanamycin and capreomycin pharmacokinetic properties. A method was developed for this study by a clinical pharmacist and biochemist at Sefako Makgatho Health Sciences University. This method was established to identify the kanamycin within the serum, where the method of identification of capreomycin within the serum is already described.

Once the levels of the drugs have been measured with an LC-MS, pharmacokinetic parameters are calculated. From these parameters, dosages can be adjusted. TDM allows the individualisation of dosing strategies to allow for a higher percentage of the population to achieve ideal concentrations compared to patients who receive a fixed dosing strategy (Avent, Rogers, Cheng & Paterson, 2011). Drug dosages are calculated according to patients' differences regarding pharmacokinetic factors and inter-patient variability (Clark et al., 2012). In some instances, dosage adjustments, or TDM can optimise individual dosages and reduce adverse effects (Kang & Lee, 2009). It would be ideal to understand the pharmacokinetic properties in patients with DR-TB and subsequently adjust medication regimens possibly to improve efficacy and reduce toxicity.

3.5. Pharmacokinetic Properties of Kanamycin and Capreomycin

There are very few studies and a dearth of literature identifying the ideal pharmacokinetic levels of kanamycin and capreomycin, specifically in patients with DR-TB. Aminoglycosides, such as kanamycin, are a well-known and efficacious category of antibiotics (Huth, et al., 2011) and thus used to treat DR-TB. Capreomycin, a polypeptide, is also a second line injectable drug used to treat DR-TB, yet it is used generally for those patients who have had previous exposure or resistance to kanamycin and streptomycin (Reisfeld et al., 2012).

3.5.1. Kanamycin

There are variations between the reported pharmacokinetics properties of kanamycin as well as aminoglycosides in general. However, the various studies were conducted on individuals with different health statutes. Kanamycin pharmacokinetic levels were obtained in patients with MDR-TB with and without HIV infection (Mugabo et al., 2015). Mugabo et al. (2015) identified an ideal peak range from previous studies in healthy participants and one study in HIV negative patients with MDR-TB of between 20 μg/ml to 35 μg/ml, and a trough of below 10 μg/ml to prevent toxicity. The volume of distribution was 5 ℓ/h to 6 ℓ/h in healthy patients and 17 ℓ/h to 23 ℓ/h in HIV negative patients with MDR-TB. Yet, in their study on patients with MDR-TB, the mean plasma concentrations after 24 hours of administration were 1.27 μg/ml and 1.97 μg/ml for HIV positive and negative patients respectively. After 24 hours, there was an undetectable amount of kanamycin in the blood (0.05 μg/ml) which could demonstrate the insufficient amount of kanamycin in the blood after 24 hours of the previous dosing. Looking at HIV-positive and HIV-negative patients, the peak levels were 16.35

μg/ml and 18 μg/ml respectively. The low concentration at the time the drug administration is completed (C_{max}) could have resulted in reduced DR-TB outcomes. The median dose for this study was 18.9 mg/kg for both HIV-positive and HIV-negative patients. Also, kanamycin was administered with other MDR-TB drugs to all patients. Lamivudine, stavudine, and efavirenz were also given to some of the HIV-positive patients. None of these other drugs affected the metabolism, distribution and renal elimination of kanamycin (Mugabo et al., 2015).

In another study on healthy participants, the half-life was 3.2 (SD ±1) hours for kanamycin, and the apparent volume of distribution for kanamycin was 30.4 (SD ±9.8) (Park et al., 2015). This volume of distribution is different to that reported by Mugabo et al. (2015), however, this study looked at healthy participants (Park et al., 2015). In another study (Mugabo et al., 2015) on MDR-TB patients using kanamycin, the volume of distribution was 38.6 ℓ/h 2 in HIV-negative patients and 50.18 ℓ/h in HIV-positive patients, as the absorption has been shown to be different in HIV-positive and HIV-negative patients. These figures on both HIV-positive and HIV-negative patients are similar to the figure by Park et al. (2015) of 30.4 ℓ/h and significantly higher than the volume of distribution in this current study of 2.5 ℓ/h for kanamycin. While the volume of distribution is significantly smaller in this study, the half-lives were significantly larger than expected, as it was compared to 3.2 ℓ/h in healthy participants (Park et al., 2015) and 1.67 in MDR-TB HIV negative patients and 1.29 ℓ/h in MDR-TB HIV-positive patients (elimination half-life) and 4.45 in MDR-TB HIV-negative patients and 4.62 ℓ/h in MDR-TB HIV-positive patients (absorption half-life) (Mugabo et al., 2015). The long-term outcomes of patients with variable pharmacokinetics are unknown, as relapse or reoccurrence of TB, is common, and the reasons are not understood fully (Millet et al., 2013).

The pharmacokinetics of various aminoglycosides (kanamycin, gentamicin, tobramycin, amikacin, sisomicin, netilmicin) are also discussed by Pechere and Dugal (1979). They placed emphasis on the multi-compartmental characterisation of aminoglycoside kinetics, especially as it relates to specific inexplicable observations such as tissue accumulation and deferred elimination. The primary route of elimination for aminoglycosides is glomerular filtration, and aminoglycosides undergo some tubular reabsorption (Pechere & Dugal, 1979). Aminoglycosides are small, hydrophilic molecules with a volume of distribution similar to extracellular fluid volume and clearance proportional to glomerular filtration rate (Roberts, Norris, Paterson et al., 2012). The penetration of aminoglycosides into the cerebrospinal fluid, bronchial secretions, and biliary tract remains somewhat random, dependent on the underlying diseases. Due to the almost exclusive excretion from the body by glomerular filtration, impairment of renal function significantly affects the elimination rate of aminoglycoside antibiotics. The predictive potential of nomograms can be significantly improved by consideration of some physiological parameters such as sex, age, lean body mass, haematocrit and characterisation of disposition kinetics by multi-compartmental models. However, definite serial monitoring of aminoglycoside concentrations in serum appears to be the most reliable method for TDM (Pechere & Dugal, 1979). Also, the volume of distribution per kilogram of body weight is somewhat smaller in obese and dehydrated subjects than in healthy patients which can lead to overdosing when dosages are calculated according to body mass (Pechere & Dugal, 1979; Droege, Van Fleet & Meuller, 2016). Alterations in the volume of distribution can be extensive in conditions leading to unstable or unknown fluid balances (e.g. sepsis of burn injuries), resulting in a reduced peak concentration if the dose is unchanged. With concentration-dependent antimicrobials, an increased volume of distribution will reduce the ability of a prescribed dose to achieve a target C_{max} (Roberts et al., 2012).

Yet, as aminoglycosides are hydrophilic, the doses should be based on body weight or adjusted body weight in obese patients. The volume of distribution of aminoglycosides in critically ill patients is generally low (Droege et al., 2016). Anaemia, fever, hypoxemia and significant burns are other pathological states which notably influence the pharmacokinetics of aminoglycosides (Pechere & Dugal, 1979).

There are various studies on aminoglycosides, but not necessarily on kanamycin and capreomycin. As kanamycin falls under the class of aminoglycosides, these studies can still assist with the understanding of kanamycin (and although not an aminoglycoside, capreomycin as well due to the similar structure). The pharmacokinetics of gentamicin were described in critically ill patients with acute kidney dysfunction (Roberts et al., 2010). Dosages varied between 3 mg/kg to 7 mg/kg. The plasma half-life of gentamicin during extended daily diafiltration (EDD-f) (a hybrid therapy that delivers a gentle yet effective diffusive and convective treatment for patients with acute renal failure) was 13.8 hours, whereas it was 153.4 hours without EDD-f. The Monte Carlo simulations propose that dosing with 6 mg/kg every 48 hours either 30 minutes or 1 hour before the commencement of EDD-f results in 100% realisation of the target maximum concentration drug in plasma (<10 mg/litre) and ample attainment of the target area under the concentration-time curve from 0 to 24 hours. In summary, this showed dosing of gentamicin 30 minutes to 1 hour before the commencement of an EDD-f treatment enables attainment of target peak concentrations for maximal therapeutic effect while enhancing drug clearance to minimise toxicity (Roberts et al., 2010). This study showed that the dosing and pharmacokinetics of a specific aminoglycoside could vary greatly depending on the treatment of the illness and other medications used in combination. Therefore, it further enhances the necessity to establish the pharmacokinetics in patients with DR-TB, and not only on healthy participants, or with other disorders. Aminoglycoside dosing for critically ill patients (for example gentamicin at 7

mg/kg) with normal renal function is suggested, where possible, to target C_{max}: MIC ratio of 10 and monitor the trough and aim for undetectable plasma concentrations. Further suggestions for patients with moderate to severe renal dysfunction in this critically ill population is also suggested to use high doses where possible and monitor the trough thereafter (36 to 48 extended hourly interval dosing acceptable). In these patients, MIC data can guide dosing if available with dose reductions (Roberts & Lipman, 2009).

3.5.2. Capreomycin

Capreomycin is further explained as a polypeptide antibiotic composed of four molecular analogues, IA, IIA, IB, and IIB, with its mode of action involving ribosomal inhibition of protein synthesis (Reisfeld et al., 2012). Its action, however, is not understood fully. It is structurally similar to viomycin and is active against DR-TB (Akbergenov et al., 2011). It differs structurally from kanamycin and amikacin and thus does not always exhibit uniform cross-resistance with the aminoglycosides. It appears that capreomycin binds to, and inhibits the function of, the 16S rRNA molecule of the *Mycobacterium tuberculosis* 30S ribosomal subunit, as supported by upregulation of a methyltransferase gene and the 16S rRNA-processing protein gene. Due to its similar organisation, side effects, and mode of action, capreomycin is often compared to and grouped with aminoglycoside antibiotics, such as kanamycin. Even though capreomycin has been used for a significant number of years as an antibiotic, there is limited pharmacokinetic information on capreomycin (Reisfeld et al., 2012).

The pharmacokinetics of capreomycin was investigated by Reisfeld et al. (2012), where they conducted an exploratory study on mice with capreomycin, yet not in combination with the other DR-TB drugs. Reisfeld et al. (2012) did, however, take individual differences into account in their model of calculation. They identified an ideal peak range between 20 μg/ml to 40 μg/ml, and a trough life of below10 μg/ml for capreomycin.

In summary, there are varying reports of pharmacokinetics with aminoglycosides and capreomycin, yet they are variable, and most do not include hearing and overview treatment efficacy. More conclusive evidence is required to identify target ranges within the DR-TB population.

3.6. Aminoglycoside Pharmacokinetics and Optimization of Drug Regimen

The injectable drugs, specifically for DR-TB, appear to have variable pharmacokinetic properties which can affect efficacy and adverse effects (Clark et al., 2012). This would indicate that the aminoglycosides, specifically kanamycin, and polypeptides, specifically capreomycin, would vary in their pharmacokinetic properties as well, and thus individualisation of dosing regimens may enhance efficacy and reduce toxic events.

Yet, there is variable research regarding the outcomes of TDM with aminoglycosides (Demczar, Nafziger & Bertino, 1997; Namazi, Sagheb, Hashempour & Sadatsharif, 2016; van Altena et al., 2017). The investigation of different dosing regimens using aminoglycosides revealed controversial outcomes (Demczar et al., 1997; Namazi, et al., 2016; van Altena et al., 2017). Once-daily dosing of aminoglycosides has become popular due to apparent advantages observed with this dosing method (Conly, Gold & Shafran, 1994). However, much of the focus of this research is about in vitro pharmacodynamics of the antibacterial effect and the concentration-dependent killing and post-antibiotic effect. The various studies, as outlined, provide information regarding the potential positive outcomes of TDM, but also the lack of outcomes.

Demczar et al. (1997), demonstrate the pharmacokinetics of gentamicin at large doses (7 mg/kg) differ significantly from those at traditional doses (2 mg/kg). This study showed significance in distribution half-life and clearance between the two groups. This could have

implications for once-daily aminoglycoside literature when the C_{max} values reported are distributional and therefore show falsely high C_{max}/minimum inhibitory concentration (MIC) ratio estimates (Demczar et al., 1997). Adverse events, such as toxicity, was not reported in these groups.

The diagnosis of the patient must also be considered when investigating pharmacokinetics. This was observed in an amikacin study where pharmacokinetic factors of patients in intensive care unit (ICU) on amikacin with different diagnoses were compared. These groups included sepsis, trauma, pneumonia and 'other'. The ICU patients were found to have increased values for the amikacin volume of distribution (0.52 ± 0.21 litres/kg), and the septic and trauma patients showed higher values for the amikacin volume of distribution. This highlights the fact that the clinical diagnosis can also impact the pharmacokinetics (de Gatta et al., 1996). Thus, patients with DR-TB may be displaying different kinetics to those with other infections mentioned above. These differences of diagnosis – highlights the importance for individualisation of treatment. These studies provide evidence for the possible positive effects of optimising dosage regimens of aminoglycosides and the need for obtaining more evidence regarding the ideal pharmacokinetic properties in these patients.

Although Heychendorf et al. (2014) does not mention the personalisation of drug therapy through pharmacokinetics, they describe the necessity of the individualisation of drug therapy and duration for participants. They describe the importance of searching for various host markers from a range of procedures, including clinical scores (general characteristics of the patient), imaging, immunological markers (cytokines and proteins) and X-Omics (analysis of metabolites, proteins, or transcription products from blood products, urine, or sputum can provide disease stage-specific molecular patterns).

Amikacin pharmacokinetics were measured in Iran, yet the treatment outcomes of patients with various illnesses were examined and not necessarily toxicity (Namazi et al.,

2016). The dosage was calculated according to conventional methods, and the prescribed dose was correct in 25% of the patients. Treatment failure occurred in 19% of the patients, and 76% had renal failure. Dosage adjustments occurred initially in 19% of the patients, yet 57% of patients needed dose readjustment, and only 6.5% were adjusted. Desired peak and trough concentrations were obtained in 38% and 45% of the patients, respectively. In 52.2%, peak levels were below the therapeutic level. Nevertheless, 89% responded to treatment successfully (Namazi et al., 2016). This shows that sometimes, in cases, treatment success may be achieved without ideal peak and trough levels. This study, however, was not for DR-TB patients, and re-infection was not discussed. Furthermore, the findings with regards to the low peak levels could yield important data with regards to the possibility of the low cure rate of DR-TB and reinfection at later stages. Preliminary studies show that Resuscitation-promoting factors (Rpf), which are peptidoglycan-hydrolysing enzymes, are required for the resuscitation of non-replicating bacilli and pathogenesis in a murine tuberculosis infection model. They are proteins produced by MTB that accelerate mycobacterial growth. Although this model is ill-defined in human infection, it is possible that Rpf plays a role in human tuberculosis pathogenesis. From the mouse models, Rpf supports bacterial survival and reactivation of TB. Also, the bacilli may be dependent upon Rpf for growth for the outcome of human tuberculosis. These Rpf are indiscernible to the conventional culture and is enhanced progressively in relative terms during chemotherapy, indicating a form of phenotypic resistance that may be significant for both chemotherapy and transmission (Mukamolova, Turapov, Malkin, Woltmann & Barer, 2010; Rosser, Stover, Pareek & Mukamolova, 2017). Therefore, these low peak levels could indicate, that although patients may culture covert on the conventional testing methods, these proteins may still be present, and responsible for the reinfection at a later stage, and thus the low peak levels could, in fact, correlate to poor outcomes.

Another study investigated the use amikacin to treat MDR-TB. Peak and trough levels were not predictors in the classification of ototoxicity (Modongo et al., 2015). Probit analysis of the amikacin study revealed that the probability of ototoxicity occurring increased sharply after six months of therapy to near maximum at nine months. This study showed that cumulative AUC and duration of drug therapy is more of an indicator of ototoxicity, rather than peak concentrations (Modongo et al., 2015).

A study conducted in the Netherlands looked at TDM of amikacin and kanamycin in patients with MDR-TB or XDR-TB. Serum levels as well as well as cumulative dose and dose per kg were collected (van Altena et al., 2017). The peak levels were obtained 30 minutes post the infusion, with the trough being obtained immediately before the infusion. The aminoglycoside dose was adjusted based on an amikacin and kanamycin concentration and MIC. Audiometry was obtained up to 8 kHz with a 20 dBHL reduction in a hearing threshold from bassline, irrespective of the ear. Treatment outcome was evaluated two years' post completion of the treatment. The patients received their dose five times a week or three times a week (post the five time a week regimen). Within the first three weeks, dosage changed for 18 patients based on serum concentrations. Three participants had an increase in dosage and dosage decreased in 15 participants. Audiometry results were available in 87.5% of patients, generally at the start of the aminoglycoside treatment and after that every 3 – 4 weeks. The results of the audiometry showed a hearing loss in 11.3% of patients, predominantly at higher frequencies (4 and 8 kHz). The mean hearing loss was 37.5 dB (range 25 dB – 50 dB) at 4 kHz and 46.1 dB (range 25 dB – 70d B) at 8 kHz. Cumulative dose, dose per kg bodyweight, duration, bodyweight, gender, age, and BMI did not correlate with the occurrence of ototoxicity. This may explain the fact that the dosage was guided by the C_{max}/MIC in individual patients since the C_{max}/MIC correlates to the efficacy of aminoglycosides (van Altena et al., 2017).

In South Africa, the administration of the standardised DR-TB regimen occurs across four weight bands to accommodate the formulations available in the country while complying with the international requirements for minimum, maximum and average dose per kilogram (NDoH, 2011). This current administration is not based on individual pharmacokinetic parameters, however, with the knowledge of pharmacokinetics, pharmacodynamics, and pharmaceutics, TDM enables the assessment of the efficacy and safety of a particular medication, in this case, kanamycin and capreomycin. Patients taking kanamycin and capreomycin for DR-TB should not be exposed to any higher risk of toxicity than justified by the need for the drug, nor obtain any less of the drug that is needed minimally for its effect (Touw et al., 2009). However, the pharmacokinetics need further understanding in the DR-TB population; with regards to relationships to toxicity and efficacy of treatment in this population before TDM would be considered as the standard of care.

Chapter 4: Ototoxicity

This chapter describes ototoxicity; its definition, possible mechanisms of action as well as the incidence. It then continues to describe ototoxicity in the DR-TB population as well as the impact it is having, specifically in the South African population. Subsequently, various methods of monitoring and trends are described, and trends, both internationally and nationally are mentioned. Therapeutic drug monitoring with aminoglycosides is discussed with the possibility of it used for ototoxicity monitoring and management. The chapter concludes with the summary and brief rationale for this study.

4.1. Overview

Toxicity due to medication can cause nephrotoxicity and cochleotoxicity/ vestibulotoxicity. Ototoxicity is defined as a toxic or poisonous reaction to medication causing damage to the inner ear, the auditory system, and/or the vestibular system, which often results in hearing and balance difficulties (Frymark et al., 2010).

4.1.1. Ototoxicity, cochleotoxicity and vestibulotoxicity

Ototoxicity is caused by medications such as cancer chemotherapeutics, loop-inhibiting diuretics, salicylate analgesics, aminoglycosides, or a combination of these agents (Konrad-Martin et al., 2005). Ototoxicity has also been recorded in some polypeptides (e.g. capreomycin), which is similar in structure to aminoglycosides (Akbergenov et al., 2011).

Cochleotoxicity research supports the notion that the damage is initially occurring to the outer hair cells (OHC) at the basal end of the cochlea. Here, the high frequencies are transduced, and thus cochleotoxicity initially affects the ability to hear high-frequency sounds. With the prolonged exposure to the ototoxic drug, damage progresses to the apical

end of the cochlea which is responsible for the processing of low-frequency sounds (Peterson & Rogers, 2015). Degeneration of nerve fibres, spiral ganglion neurons and supporting cells are secondary to hair cell damage. Strial degeneration is also described however it is unclear whether strial degeneration is a secondary or primary effect of the aminoglycosides (Guthrie, 2008). Cochleotoxicity is generally irreversible as hair cells in humans are not yet capable of regeneration (Peterson & Rogers, 2015).

Vestibulotoxicity is the ability of a substance to destroy or damage the structures and function of the labyrinthine hair cells and their connections through the eighth cranial nerve to the central nervous system (Selimoglu, Kalkandelen & Erdogan, 2003). The initial and most extensive damage occurs at the apex of the cristae and striolar regions of the maculae. The damage can extend to the periphery of the vestibular receptor, and additional injury can occur to the otoconial membrane and the otolith structures (Selimoglu et al., 2003). The effect of vestibulotoxicity is normally permanent and may affect an individual's quality of life negatively (Rogers & Peterson, 2011), as balance disorders can affect social, family and professional activities (Patatas, Ganança & Ganança, 2009).

There are varying reports regarding the onset, degree, and progression of ototoxicity. Ototoxic side effects have been shown to occur within days or weeks after systemic application and are often bilateral in presentation (Huth et al., 2011).

The differences in reports regarding the degree, onset and progression can be due to intrinsic and extrinsic factors (Peterson & Rogers, 2015) while the different definitions used to define and report ototoxicity (Huth et al., 2011) could contribute to the variance. Different studies use different protocol and classifications, as some include ultra-high frequencies, where others do not (Sharma, Bhagat, Verma, Singh & Singh, 2016; Fausti, Henry, Schaffer et al., 1992). Different methods of testing would identify different percentages of hearing loss. Also, there are various ways to classify significant hearing loss, such as the different

grading scales (see section 4.7.4). Different classifications of hearing loss could result in the varying reports on ototoxicity.

4.1.2. Intrinsic factors

Intrinsic factors may include previous treatment with ototoxic medications (Wang et al., 1999), prolonged exposure to ototoxic medication (Peloquin et al., 2004), renal impairment (Harris & Heinze, 2015), other illnesses (Bisht & Bist., 2011), genetic susceptibility (Fischel-Ghodsian, 1999), poor nutrition (Hoffman, Whitworth, Jones & Rybak, 1987), advanced age (Paterson, Robson & Wagener, 1998), excessive noise exposure (Schellack & Naude, 2013), pre-existing hearing loss and vestibular dysfunction (Mudd, Glatz, Campbell & Gatz, 2016) and HIV (Khoza, 2010).

Wang et al. (1999) explain the effects of previous treatment with ototoxic medication, as they demonstrated that ototoxicity might persist for up to one year after discontinuing the drug. Therefore, the drug may still be having an ototoxic effect after treatment. Furthermore, having aminoglycosides in one's system, in addition to new aminoglycosides, can increase the cumulative dosage of the drug which can enhance ototoxicity (Peloquin et al., 2004).

Prolonged exposure to ototoxic medication is linked to the destruction of the OHC in the organ of Corti (Rybak & Ramkumar, 2007). This prolonged exposure can also result from a large cumulative dose (Peloquin et al., 2004). Renal impairment can potentiate hearing loss from ototoxic medication in a similar way, in that impaired renal function affects the excretion of the drug, and so result in higher serum levels and thus prolonged half-life (Rybak & Ramkumar, 2007; Harris & Heinze, 2015).

Various illnesses, such as the presence of infected emboli, hypoxia, fever, and dehydration can influence ototoxicity (Bisht & Bist, 2011). Diabetes mellitus has also shown to cause hearing impairments (Kakarlapudi, Sawyer & Staecker, 2003) as well as HIV, which can influence ototoxicity. Human Immunodeficiency Virus can have a direct and indirect

effect on the auditory system. Opportunistic effects are deemed indirect by some; while others feel that these auditory manifestations are a direct effect on the compromised immune system. The sensorineural hearing loss has been associated in a direct manner causing neural disturbances of the vestibulocochlear nerve; however, these neural disturbances can also be caused indirectly by opportunistic illnesses such as cytomegalovirus (Friedmann & Arnold, 1993; Khoza & Ross, 2002). Hearing loss with HIV patients has shown to range in type, from conductive to sensorineural as well as retrocochlear or central (Bankaitis, 1996; Khoza, 2010). However, many people with MDR-TB have HIV, and thus it is difficult to separate the effects of the MDR-TB medication from the effects of HIV (Brits et al., 2012). There is some evidence that some ARV drugs used for the management of HIV may be ototoxic (Khoza-Shangase, 2011). Also, pre-existing hearing loss and vestibular dysfunction, although not an illness, can also enhance ototoxicity (Mudd et al., 2016). Pre-existing hearing and vestibular dysfunction result in a vulnerable auditory system which makes it more susceptible to ototoxicity.

There is also a genetic link to aminoglycoside ototoxicity (Fischel-Ghodsian, 1999). A study by Guan, Fischel-Ghodsian and Attardi (2000) showed that the A115G mutation in mitochondrial 12S rRNA is associated with non-syndromic and aminoglycoside-induced deafness (Guan et al., 2000; Rybak & Ramkumar, 2007). Likewise, there are another known mitochondrial mutations which are linked to aminoglycoside-induced hearing loss namely A1555G, C1494T, T1095C, T1291C, 961delT+C(n) and A827G; A1555G is, however, the most common (Harris & Heinze, 2015).

Poor nutrition can play a role in hearing loss, as seen in a study by Hoffman et al., 1987) where chinchillas deprived of food for 48 hours prior to the administration of a combined dose of ethacrynic acid (10 mg/kg) and kanamycin (100 mg/kg) suffered a profound hearing loss, when compared to animals that were fed, who showed a lesser degree

of hearing loss. Poor nutrition places the auditory system under stress, and combined with the aminoglycosides could enhance the ototoxicity. Houston et al., (1999) also investigated how poor vitamin B-12 and folate levels may be associated with age-related auditory dysfunction. This could potentially also affect hearing loss from other causes, such as aminoglycosides. According to the trading economics statistics of the last three months in 2016, 26.5% of South Africans were unemployed (Trading Economics, 2017). Therefore, poverty and poor nutrition is a reality for many South Africans.

As ageing patients are at risk for presbycusis (Lin, Thorpe, Gordon-Salant & Ferrucci, 2011), it is possible, that this increased age, which, if combined with an ototoxic aminoglycoside, could place an already vulnerable system under more stress. Further, animal studies have suggested that the susceptibility to aminoglycoside -related nephrotoxicity in the elderly arises from the declining renal excretory function in this age group. It is possible that this is due to the impaired capacity for cellular repair and regeneration in the elderly (Paterson et al., 1998).

4.1.3. Extrinsic factors

Extrinsic factors are not as vast and may include concomitant treatment with other ototoxic or nephrotoxic drugs (Peloquin et al., 2004), dosage (Schellack & Naude, 2013), health practitioners' knowledge (Peterson & Rogers, 2015) and the attitude of the staff (Peterson & Rogers, 2015).

Excessive noise exposure can also enhance ototoxicity. Aminoglycosides block the ion channels which may be mediated via endocytosis or possibly aminoglycosides. This mechanism might be due to the aminoglycosides blocking the depolarising transduction current of the mechanoelectrical transducer (MET) channel. The MET channel is located in the stereocilia and can function as a one-way valve, promoting intracellular accumulation of

the aminoglycosides. Acoustic stimulation may aggravate this as it may enhance the aminoglycoside uptake (Schellack & Naude, 2013).

While other illnesses were included in the intrinsic factors, concomitant treatment with other ototoxic or nephrotoxic drugs in considered extrinsic. Other ototoxic drugs result in a more extensive cumulative build-up of the drugs, and this larger cumulative dose has been associated with ototoxicity (Peloquin et al., 2004). The ototoxic loop diuretics can potentiate ototoxicity as well (Rybak & Ramkumar, 2007).

The total administered dose and dosing frequency links to the toxicity of the aminoglycosides. Dosages twice daily or more frequently are associated with more ototoxicity in comparison to once daily dosing (Schellack & Naude, 2013). In contrast, Peloquin et al. (2004) looked at the incidence of toxicities associated with two recommended dosing regimens (daily vs three times per week of intravenous streptomycin, kanamycin, or amikacin) in TB patients and found that the magnitude of the dose and frequency of administration were not associated with ototoxicity, but ototoxicity was associated with a more substantial cumulative dose (Peloquin et al., 2004).

Health practitioners' knowledge of and attitudes to cochleotoxicity, as well as the availability of diagnostic/monitoring services, are important in reducing ototoxicity (Peterson & Rogers, 2015). It is essential that the healthcare practitioner has adequate knowledge about ototoxicity in order to manage and refer the patient appropriately (Peterson & Rogers, 2015) as well as their attitudes can determine whether the patient seeks help when noticing symptoms of hearing loss. A study in South Africa found that nurses caring for TB patients were found to be authoritarian, scolding and frustrated. These behaviours can deter patients from reporting symptoms (Peterson & Rogers, 2015).

These intrinsic and extrinsic factors are numerous, and all need consideration for patients at risk to develop ototoxicity, specifically those with DR-TB. By understanding these factors, one may potentially be able to facilitate a reduction of ototoxicity.

4.2. Theories: Aminoglycoside and Polypeptide Ototoxicity

Aminoglycosides are often toxic; to both the kidney (nephrotoxicity) and the inner ear (ototoxicity). Nephrotoxicity, however, is often reversible, while ototoxicity is generally permanent (Huth et al., 2011), demonstrating the importance of understanding and managing this ototoxicity due to its permanence.

Furthermore, aminoglycosides and some polypeptides are reported to cause damage to both the auditory and vestibular system (Dooley et al., 2012; Huth et al., 2011; Roongruangpitayakul & Chuchottaworn, 2013). In some instances, the ototoxicity and vestibulotoxicity were reversible, particularly with capreomycin (Roongruangpitayakul & Chuchottaworn, 2013), Yet in most cases, it seemed to be irreversible and permanent (Dooley et al., 2012; Peterson & Rogers, 2015). Typically, either the auditory system or vestibular system is affected more than the other (Hutch et al., 2011). For example, gentamicin and tobramycin are predominantly vestibulotoxic, whereas neomycin, kanamycin, and amikacin are mainly cochleotoxic (Huth et al., 2011). Although the majority of reports show capreomycin as cochleotoxic (Dooley et al., 2012; Peterson & Rogers, 2015), there are reports of it being vestibulotoxic too (Roongruangpitayakul & Chuchottaworn, 2013).

Studies indicate that ototoxicity can occur as early as 72 hours after aminoglycoside administration (Konrad-Martin et al., 2005). Ototoxicity may also continue after the termination of aminoglycoside treatment as aminoglycosides can remain within the cells of the inner ear for up to six months; thus, ototoxic injury and associated hearing loss may

progress for weeks following cessation of treatment (Harris & Heinze, 2015). Wang et al. (1999) demonstrated that ototoxicity might persist for up to one year after discontinuing the drug.

There are various theories regarding aminoglycosides ototoxicity. There are fewer however on polypeptide ototoxicity. Yet, polypeptides, specifically capreomycin and vancomycin are similar in structure to the aminoglycosides with similar mechanisms of action, and so capreomycin is often compared to aminoglycosides, due to its similar nomenclature, side effects, and mode of action, despite its structural distinction (Reisfeld et al., 2012).

As there are fewer data available on polypeptides' specific mechanism of action with regards to ototoxicity, they are likened to the aminoglycosides (Petersen & Rogers, 2015). Therefore, the aminoglycoside theories, discussed further, in this case, will be regarded as the polypeptides, specifically capreomycin.

These various theories of aminoglycoside ototoxicity, which likely do not work in isolation, but a combination of all three, include oxidative stress and free radical formation (Poirrier, Pincemail, Ackerveken, Lefebvre & Malgrange, 2010), uptake and penetration of the aminoglycosides within the cochlear cells (Xie, Talaska & Schacht, 2011) and well as drug concentrations (Touw et al., 2009).

4.2.1. Oxidative stress and free radical formation

The first theory provides evidence for oxidative stress in aminoglycoside ototoxicity (Campbell, 2004), such as with aminoglycosides used to treat DR-TB. The aminoglycosides used to treat DR-TB can cause irreversible hearing loss, as they destroy the OHC in the cochlea. The exact pathophysiological mechanism is not entirely understood (Avent et al., 2011).

Furthermore, many aminoglycosides have shown to be ototoxic and nephrotoxic as well (Rybak & Ramkumar, 2007). Some aminoglycosides are also more vestibulotoxic, such as streptomycin and gentamicin, while and others are more cochleotoxic, such as amikacin, neomycin, dihydrosterptomycin, and kanamycin (Selimoglu, 2007). This oxidative stress and reactive oxygen species formation are described particularly to those that are cochleotoxic.

Reactive oxygen species play a pivotal role in aminoglycoside ototoxicity as these aminoglycosides have been suggested to have ototoxic effects due to intracellular cytotoxic effects. Similarly, recent research suggests that these also play a role in ageing and presbycusis (Poirrier et al., 2010).

The outer hair cells in the cochlea appear to be vulnerable to reactive oxygen species injury. However, the exact way in which the reactive oxygen species enter the cochlear fluid is not understood entirely (Poirrier et al., 2010). Nevertheless, once the aminoglycosides are inside these cochlea cells, they start to generate reactive oxygen species, which is central to the destruction of these hair cells (Poirrier et al., 2010).

Aminoglycosides are considered as redox-inactive compounds, whereby the molecule is not toxic by itself but requires the redox-capacity of a transition metal ion to induce ototoxicity (Guthrie, 2008). Therefore, the generation of these reactive oxygen species involves the formation of an aminoglycoside -iron complex, which catalyses the oxidation of unsaturated fatty acids located in the plasma membrane (Poirrier et al., 2010).

In the absence of iron, arachidonic acid enriched in phosphoinositides can serve as an electron donor. In this case, aminoglycosides interfere with phosphoinositides metabolism, particularly phosphatidylinositol-biphosphate (PIP2), by binding to their polar head. This binding induces sequestration of PIP2 and therefore prevents PIP2-dependent processes, including the reduction of phosphatidylinositol-trisphosphate (PIP3) formation and thus

aminoglycosides, seem to inhibit cell survival pathways such as PI 3-kinase/Akt signalling pathway (Xie et al., 2011; Poirrier et al., 2010).

Aside from the actual reactive oxygen species formation, aminoglycosides also directly control the activity of enzymes involved in reactive oxygen species metabolism. The aminoglycosides, therefore, inhibit the antioxidant activity to protect the cochlea from reactive oxygen species potentially, or they activate inducible nitric oxide synthases producing nitric oxide (Poirrier et al., 2010).

Nitric Oxide has been suggested to be involved in hair cell death induced by gentamicin, and these aminoglycosides have also been shown to indirectly promote the activation of nitrogen oxides leading to the production of superoxide which can initiate a cascade of reactive oxygen species production (Poirrier et al., 2010).

Reactive oxygen species subsequently activates apoptotic or necrotic intracellular pathways. They promote the opening of the mitochondrial permeability pore and activate the Jun N-terminal kinases pathway leading to hair cell apoptosis. It has been shown that the inhibition of Jun N-terminal kinases pathway rescues hair cells injured by aminoglycosides (Poirrier et al., 2010).

Following aminoglycoside-induced hair cell injury, there is a progressive loss of spiral ganglion neurons because of loss of neurotrophic support from the OHCs. Neurotrophin withdrawal increases reactive oxygen species production in neuronal cell lines and spiral ganglion neurons in culture. The interaction of reactive oxygen species and free radicals with membrane phospholipids creates lipid peroxidation products that act as mediators of apoptosis (Poirrier et al., 2010).

4.2.2. Uptake and penetration of the aminoglycosides within the cochlear cells

The second theory describes the uptake of aminoglycosides whereby the aminoglycosides penetrate almost all cell types of the cochlea including those not damaged by the drugs (Xie et al., 2011). Aside from the hair cells, the areas with highest affinity for and most extended retention of aminoglycosides are the mesenchymal cells under the basilar membrane, the interdental cells of the spiral ligament, and type III fibrocytes. The glycoprotein megalin has been suggested as an aminoglycoside transporter in proximal tubules of the kidney, but its distribution in the inner ear does not match the pattern of aminoglycoside uptake and ototoxicity (Xie et al., 2011).

Various animal studies suggested an endocytotic uptake at the apex of the hair cell or uptake regulated by myosin VII-A (Xie et al., 2011). Other potential transport mechanisms include a polyamine-like transport and vesicular receptor-mediated endocytosis at the base of hair cells. Entry through ion channels such as the mechano-electrical transducer channels is another option (Xie et al., 2011; Poirrier et al., 2010). Studies have shown that gentamicin rapidly enter the marginal cells in the stria vascularis and hair cells in mice which suggests that these drugs penetrate the endolymphatic scala media of the inner ear (Poirrier et al., 2010).

Another study by Steyger and Hongzhe (2011) mentioned that systemic aminoglycosides are trafficked across the blood-endolymph barrier and preferentially enter hair cells across their apical membranes. This route is predominant over the basilar membrane entry by perilymph infusion (Steyger & Hongzhe, 2011).

From the various theories, it is possible that there is more than one mechanism of uptake. Nevertheless, it is postulated that the OHCs in the cochlea appear to be vulnerable to Reactive Oxygen Species (ROS) injury, despite the exact way in which the reactive oxygen

species enter the cochlear fluid is not understood entirely (Poirrier et al., 2010). Currently otoprotection research supports the theory of promoting antioxidant activity, and in turn protect the OHC from reactive oxygen species (Poirrier et al., 2010). It could perhaps be beneficial to fully understand the uptake of these aminoglycosides, in order to block this pathway into the OHCs and prevent the production of reactive oxygen species, rather than by destroying them (Poirrier et al., 2010).

4.2.3. Drug Concentrations

Lastly, aminoglycosides are inhibitors of prokaryotic protein synthesis at commonly accepted therapeutic concentrations (Touw et al., 2009). They exhibit concentration-dependent bactericidal activity, and intermittent doses overcome adaptive bacterial resistance (Peloquin et al., 2004). However, they may also affect the protein synthesis of cells at larger concentrations, leading to toxicity, such as ototoxicity and/or nephrotoxicity (Touw et al., 2009).

There is a dearth of literature regarding this topic. However, a few studies have been performed showing that the adjustment of dosages can reduce ototoxicity (van Altena et al., 2017; Engler, Schellack, Naude & Gous., 2015), which would indicate that drug concentration levels can be pertinent to ototoxicity. This current study investigates this topic further.

4.2.4. Summary

Therefore, with any of the above theories; the more extensive the concentration - the greater the ototoxicity. At this time, it appears that all three aspects, including the ROS, uptake of the aminoglycosides and drug concentrations should be considered as vital contributing factors to ototoxicity, and thus all should be considered in research to reduce this toxicity.

4.3. Prevalence of Aminoglycoside and Peptide Ototoxicity

Despite the resulting ototoxicity from aminoglycosides, these agents are utilised widely in developing countries because they are cost effective. The various aminoglycosides differ with regards to their toxicity profiles (Rybak & Ramkumar, 2007) and the prevalence of this cochleotoxicity differs in various populations and with different drugs (Petersen & Rogers, 2015, Davidson, Brish, Rein & Rubinstein, 1980; Youw, Tengg, Bangs, Bangs & Stephenson, 1962; Waterstrom, Bredberg, Lindquist,Lyttkens & Rask-Andersen, 1986; Al-Malky, Suri, Dawson, Sirimanna & Kemp D., 2011; Black, Lau, Weinstein, Young & Hewitt, 1976; Fausti et al., 1993). Some peptide antibiotics, despite having evidence of ototoxicity (Petersen & Rogers, 2015; Forouzesh, Moise & Sakoulas, 2009) have been studied in less detail, yet are also used to treat bacteria, such as in TB (Sagwa, 2017).

Aminoglycosides, including kanamycin, amikacin, tobramycin, netilmicin, streptomycin and gentamicin have different reports of ototoxicity (Petersen & Rogers, 2015, Davidson et al., 1980; Youw et al., 1962; Waterstrom et al., 1986; Al-Malky et al., 2011; Black et al., 1976; Fausti et al., 1993). Peptide antibiotics are numerous (Hancock & Chapple, 1999), and so only three specific peptides will be mentioned, namely capreomycin and triethanolamine (polypeptide) and vancomycin (glycopeptide) as they have indicated some ototoxicity (Forouzesh et al., 2009; Akorn, Inc. Package Insert, 2015; Daniel, Sahmkow, Munguia, Schloss & Akache, 2008). However, according to Peterson & Rogers (2015), capreomycin, a polypeptide, can have a similar effect on the auditory system as aminoglycosides.

The prevalence of cochlear damage due to aminoglycosides ranges from seven to 90% (Petersen & Rogers, 2015). This variability could be due to a potential of underreporting, as

well as the lack of distinct parameters for monitoring ototoxicity (Edson & Terrell, 1991; Petersen & Rogers, 2015). Different studies also detail different dosages and methods of monitoring, which could account for the difference in incidence (Arslan, Orzan & Santarelli, 1999). Furthermore, there are very few human and animal studies using kanamycin and capreomycin when not treating TB.

Studies with kanamycin have shown diverse results when used to treat infections (not TB). In a paediatric study, kanamycin at a relatively low dose (15 mg/kg daily for less than 17 days or a total dose of 280 mg) did not result in hearing loss (Davidson et al., 1980). This hearing loss was defined as a 20 dB decrease in hearing thresholds above 4 kHz and up to and including 8 kHz. Although, kanamycin did cause hearing loss in a much smaller case study of two infants who received dosages of more than 500 mg/kg (Youw et al., 1962). This small case study did not take other perinatal factors into account which could have contributed to the hearing loss. Kanamycin ototoxicity was further illustrated in an animal study with Guinea pigs, (Waterstrom et al., 1986) where ototoxicity was noted in the group that received 200 mg/kg per day for 21 days as well as in the group that received 60 mg/kg per days for 90 days. This study indicated how kanamycin, on raised dosages or increased periods can result in ototoxicity (Waterstrom et al., 1986).

Ototoxicity, from aminoglycosides, has been observed in various other studies (Fausti et al. 1993; Moore, Smith & Lietman, 1984). These studies, in some instances, investigated aminoglycosides in general and did not separate the different drugs (Fausti et al. 1993; Moore et al., 1984). Amikacin, an aminoglycoside often used to treat DR-TB (Sagwa, 2017), has demonstrated ototoxicity through a variety of studies. Black et al. (1976) looked at amikacin at dosages of ≥7.5 mg/kg every eight hours in patients who were leukopenic, infected with gentamicin-resistant organisms or had cystic fibrosis. They found, using pure tone audiometry (PTA), that 24% were associated with the development of high-frequency hearing

loss, which was usually bilateral. Also, the onset of cochlear damage occurred in one patient after therapy was stopped (Black et al., 1976). Hotz, Harris and Probst (1994) found a higher incidence of amikacin induced ototoxicity, at 90%, when used for more than 12 days. However, this was a small sample (10 ears), and Transient Evoked Otoacoustic Emissions (TEOAEs) were utilised in contrast to Black et al. (1976), where the use of audiometry. Lerner and Matz (1979), with a larger group using gentamicin or amikacin, found a hearing loss in 7% of those taking gentamicin and 9% on amikacin. However, as per Black et al. (1976), PTA was used in contrast to TEOAEs.

Moore et al. (1984) investigated incidence as well as risk factors for the expansion of auditory toxicity in patients receiving aminoglycosides, specifically gentamicin, tobramycin and amikacin. Ototoxicity, found in 22.3%, was found to be associated with drug therapy for a more extended period, patients who were more likely to be bacteremic, and had a higher temperature on average. The factors that did not significantly associate with hearing loss included plasma aminoglycoside levels, aminoglycoside type, furosemide use, diabetes, age, sex, renal function, initial auditory acuity, hematocrit value and shock (Moore et al., 1984). Fee (1980), while investigating tobramycin and gentamicin, found only 16.4% ototoxicity in the gentamicin sample, which also showed more toxicity than tobramycin. The hearing loss from gentamicin progressed after the discontinued drug. This incidence of gentamicin toxicity is less than Moore et al. (1984) of 22.3%, yet Moore et al. (1984) did not separate the drugs. As with Moore et al. (1984), associations between ototoxicity with high temperature and duration of therapy, and well as no associations with serum levels and age occurred. In contrast to Moore et al. (1984), Fee (1980) showed positive associations with ototoxicity with renal function and hematocrit value.

There is significantly more research on aminoglycoside ototoxicity than polypeptides, such as capreomycin. Yet, polypeptide ototoxicity, with capreomycin has been shown

through a human study (Akorn, Inc. Package Insert, 2015), and with ototopic triethanolamine polypeptide oleate-condensate in an animal (chinchilla) study (Daniel et al., 2008). Capreomycin (injectable Capastat Sulfate) resulted in a subclinical auditory loss in approximately 11% of 722 healthy patients (5 – 10 dB loss in the 4 – 8 kHz range) and a clinically apparent hearing loss in 3% of the subjects. Some audiometric changes were reversible, and cases with permanent loss were not gradual following withdrawal of Capastat Sulfate. Tinnitus and vertigo were also reported (Akorn, Inc. Package Insert, 2015). However, these losses from capreomycin were in healthy individuals, where sick patients, such as those with TB, may have other risk factors, for example, previous exposure to ototoxic medications, which would perhaps make them more at risk and susceptible to ototoxicity (Wang et al., 1999). Additionally, ototopic triethanolamine polypeptide oleate-condensate 10% was investigated in chinchillas (Daniel et al., 2008) as this composition is utilised as cerumenex, an earwax softener used in humans. Mean DPOAEs (between 1 kHz and 9 kHz) in the chinchillas were reduced from the first day of the study. This study demonstrated the possible ototoxic effects of another polypeptide other than capreomycin, however, has so far only been investigated in an animal model (Daniel, 2008).

Furthermore, vancomycin, a glycopeptide, has resulted in ototoxicity (Forouzesh et al., 2009), when investigated through a retrospective case-control analysis of audiometry results for patients on vancomycin therapy. Results showed a pattern of high-frequency hearing loss in 12% of the sample, with a trend in univariate analysis toward a higher rate with advanced age (Forouzesh et al., 2009). Although there are few human studies on peptides and polypeptides, specifically on capreomycin and vancomycin, results do indicate a relationship to ototoxicity.

There is some controversy regarding the incidence of hearing loss in various human and animal studies, yet it is evident that ototoxicity occurs. Further investigation to

understand the cause and risk factors to predict an overall definitive incidence of the hearing loss with the various aminoglycosides and polypeptides is necessary. Also, the method the monitor and define ototoxicity needs to be established in order for consistent statistics and studies.

4.4. Ototoxicity in the DR-TB Population

The inclusion of kanamycin and capreomycin as part of the international and national DR-TB treatment regimen (NDoH, 2013; WHO, 2016b), places patients with DR-TB at risk for ototoxicity (Jacobs & Ross, 2012; de Jager & van Altena, 2002; Duggal & Sarkar, 2007; Ramma & Ibekwe, 2012; Sturdy et al., 2011; Sagwa et al., 2015; Melchionda et al., 2013; Akbergenov et al., 2011).

Various studies reported varying degrees of ototoxicity in the DR-TB population (Harris et al., 2012), yet these studies defined and reported ototoxicity differently. Harris et al. (2012) showed 57% of patients with MDR-TB developed high-frequency hearing loss. Similarly, Ramma and Ibekwe (2012) found 47% to show a hearing loss in a cross-sectional study of adult MDR and XDR-TB patients in Cape-Town. Yet, Jacobs and Ross (2012) found 28.7% of patients treated with amikacin or kanamycin for DR-TB developed hearing loss and vestibular disturbances. This study did not describe the audiological tests and frequencies measured (Jacobs & Ross, 2012).

Furthermore, de Jager and van Altena (2002) showed even less ototoxicity in patients treated with amikacin, kanamycin and/or streptomycin, as measured by PTA. This hearing loss was found in 18% of the total population treated with aminoglycosides, while 15.6% were from kanamycin. This contrasts with Sagwa et al. (2015), who showed that amikacin appeared to be more ototoxic than kanamycin, yet also found a much higher percentage of hearing loss in MDR-TB patients, at 58%. This incidence is similar to the studies by Harris et

al. (2012) and Ramma and Ibekwe (2012). Sagwa et al. (2015) presented a unique report, as no other studies could be found showing that amikacin is more toxic than kanamycin. Most of the hearing loss in their study was bilateral (83%), with 32% classified as mild, 23% as moderate, 16% as moderate-severe, 10% as severe and 15% as profound in severity (Sagwa et al., 2015).

Ototoxicity has been noted in many other DR-TB studies. Duggal and Sarkar (2007) looked at patients on amikacin, kanamycin, and capreomycin, and found 18.75% of the patients acquired sensorineural hearing loss involving higher frequencies while 6.25% were involved of speech frequencies also. No threshold shift (better or worse) was seen after discontinuation of therapy, and the hearing losses were permanent. In addition, Sturdy et al. (2011) found 28% of patients experienced ototoxicity in their retrospective study on injectable antimicrobials for MDR-TB in the UK. The type of injectable antimicrobial varied, as with many other studies.

Interestingly, shorter treatment (approximately three to six months) was observed in London (Melchionda et al., 2013). Amikacin was used, and trough levels were consistently within the target range. Hearing was tested between 0.25 kHz and 8 kHz. An audiologically detectable hearing loss occurred in seven patients. Only four had a gradable hearing loss according to the Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale. Despite the shorter regimen, there have been no cases of TB reactivation since treatment completion in the reported study (Melchionda et al., 2013).

Bardien et al. (2009) further describe how aminoglycosides persist in the inner ear tissues for six months or longer after administration and can cause further hearing loss. This does not always occur, as seen in the study by Duggal and Sarkar (2007). Despite these adverse effects, in this case, ototoxicity, these aminoglycosides and capreomycin are utilised for the treatment of MDR-TB in South Africa (NDoH, 2011). More so, the ARV medication

may further augment hearing loss (Khoza, 2010). The South African health professionals are therefore potentially facing the risk of a significant proportion of the population acquiring permanent drug-induced hearing loss due to these aminoglycosides and capreomycin used to treat MDR-TB (Bardien et al., 2009).

In addition to the aminoglycosides and capreomycin, there is conflicting evidence indicating that antiretroviral drugs, used to treat HIV, may be ototoxic. This is of particularly relevant, as 50% of TB patients are HIV positive in South Africa, yet this statistic does not differentiate between TB and DR-TB (Harris & Heinze, 2015). This potential ototoxicity has been described with an in-vitro study which yields evidence of auditory toxicity resulting from HIV drugs (Thein, Kalinec, Park & Kalinec, 2014). In contrast, human studies are difficult to retrieve conclusive evidence, as it is challenging to separate effects of the HIV itself from the effects of the HIV drugs (Khoza, 2010).

Thein et al. (2014), with an in vitro study, described how the cocktails of HIV drugs decreased auditory cells' viability, specifically the HEI-OC1 auditory cells, with high significance. Epzicom® was shown to be most affected while Truvada® was the least. In contrast, a study conducted on HIV patients in a real-life setting found no statistically significant relationship between ARVs and hearing loss (Vieira, Greco, Teófilo & Gonçalves, 2008). Furthermore, Khoza (2010) conducted a systematic review on hearing loss in adults with HIV with a particular focus on the possibility of ototoxicity of ARVs. This review highlighted points such as ART ototoxicity reported is mainly from case reports as well as the lack of sensitive tools to assess ototoxicity in more significant samples (Khoza, 2010). As there is evidence of possible ototoxicity from ARVs, despite it being conflicting and weak, HIV and its treatment must be considered as a possible factor contributing to the ototoxicity in the DR-TB population. Furthermore, the proportion of known HIV-positive TB patients globally on ART was 78% globally according to the WHO TB report in 2016. This HIV

treatment and its adverse effects must be considered when describing hearing loss in DR-TB patients.

4.5. Configuration of this Ototoxic Hearing Loss

Hearing loss resulting from aminoglycosides is usually gradual, bilateral and symmetrical (Harris & Heinze, 2015; Schmidt, Knief, Lagosch, Deuster & am Zehnhoff-Dinnesen, 2008). However, asymmetry has been noted in some instances (Huizing & de Groot, 1987), with possible explanations presented below. The degrees of the hearing losses tend to differ, and details regarding the degree of hearing loss are not always reported.

Moreover, with increased exposure to the drugs, this high-frequency hearing loss often progresses to involve the lower frequencies. As aminoglycosides can stay within ones system for six months to a year after completion of aminoglycoside drug therapy, hearing loss can continue to occur after the cessation of treatment (Harris & Heinze, 2015). These hearing losses are likely to cause a hearing handicap, defined as the disadvantage imposed by a hearing impairment on a person's communicative performance in the activities of daily living (American Speech-Language-Hearing Association, 1981).

4.5.1. Degree

A typical audiogram from an MDR-TB patient may appear as per Figure 4.1. This figure displays the initial high-frequency hearing loss progressing to include the lower frequencies.

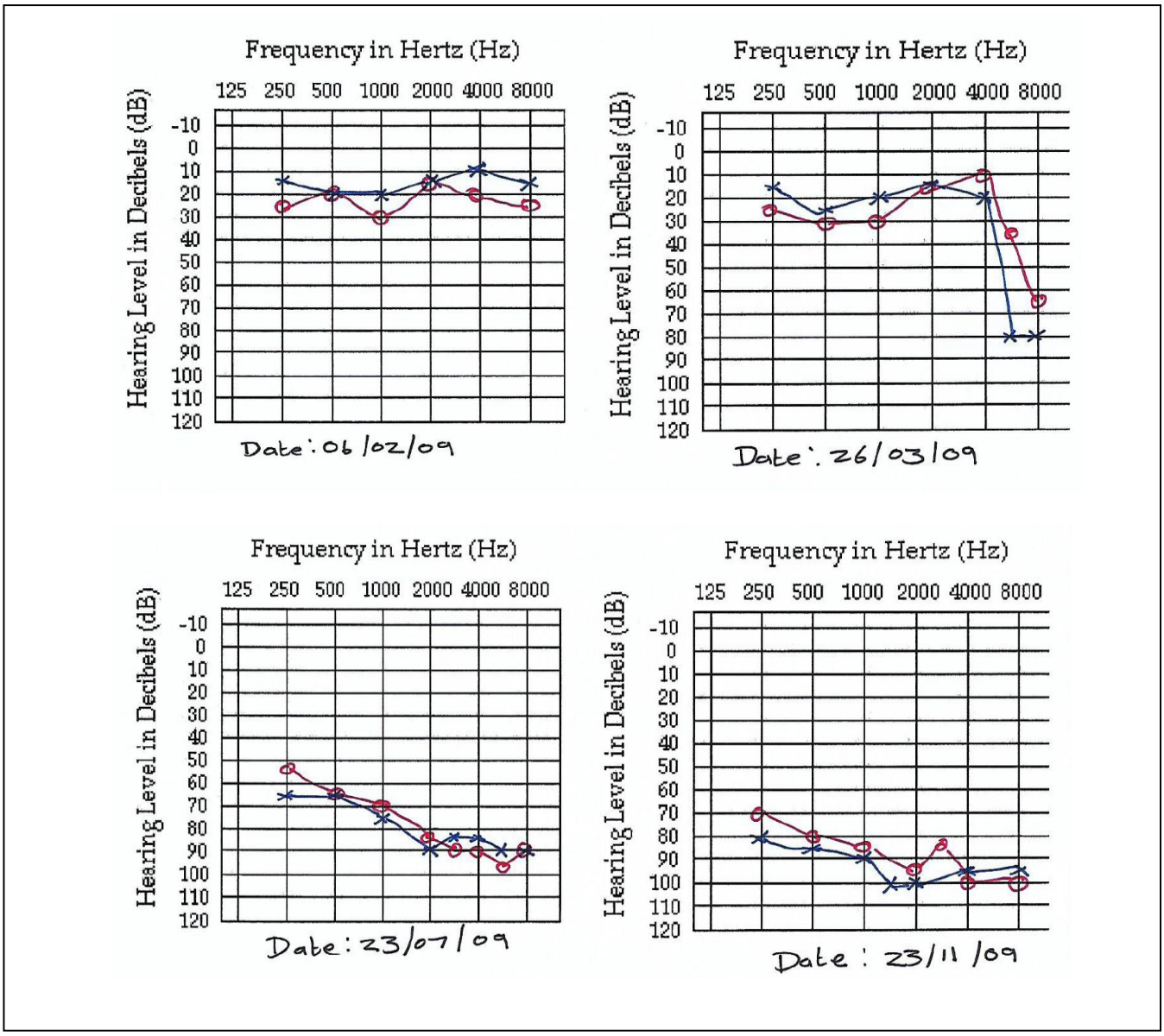

Figure 4.1. Baseline and follow-up audiograms of a patient on treatment for MDR-TB (Adapted from Harris & Heinze, 2015, p. 3)

High-frequency nature aminoglycosides induced hearing loss described in various studies (Sharma et al., 2016; Javadi et al., 2011; Fausti et al., 1992). Although they mostly report the bilateral hearing loss (Sharma et al., 2016; Javadi et al., 2011) in some instances, unilateral hearing loss is described, which depicts asymmetry.

This high-frequency loss was observed in an MDR-TB study using kanamycin in India (Sharma et al., 2016). Of the 100 patients examined, ototoxicity was found in 18% of participants, with majority displaying high-frequency hearing loss. The hearing loss was also

mainly bilateral, yet the hearing loss was unilateral in 5% of these patients (Sharma et al., 2016). High-frequency hearing loss was described further in a paediatric TB study (Ghafari, Rogers, Peterson & Singh, 2015). Furthermore, high-frequency hearing loss was seen in the majority of the patients that experienced ototoxicity with 62% being bilateral and 48% being unilateral (Javadi et al., 2011). All these studies only tested up to 8 kHz. However, when testing frequencies higher than 8 kHz (9 kHz to 20 kHz), as with Fausti et al. (1992), it was possible to identify an early change in hearing in 82% of the ears.

4.5.2. Laterality and symmetry

Unilateral and asymmetrical hearing loss is not understood in relation to ototoxicity, yet it has been reported in the above studies. Various ideas have however been proposed. McFadden (1993) discusses two main differences known in hearing sensitivity, namely gender and ear when measured with OAEs. McFadden (1993) describes this as females being more sensitive than males, and right ears being more sensitive than left ears. This right ear advantage is described mainly in individuals' exposure to intense sounds, where the right ear displayed a lesser hearing loss than the left ears. However, the difference of this was minimal; the magnitude of the right-ear advantage in sensitivity was rarely more than 2-4 dB at a given frequency, and it differed as a function of several variables. This article noted the plausibility of a developmental linkage between efferent-based asymmetries insensitivity and asymmetries in adult cortical lateralisation (McFadden, 1993). Furthermore, in a study by Chung, Masoon, Gannon and Willson (1983), with a participant group of more than 50 000 people, differences of about 1.5-2.5 dB were noted for male adults in the range 2-6 kHz between the ears. The right ear always appeared to have the superior hearing levels.

A variety of studies by Khalfa, Morlet, Micheyl, Morgon and Collect (1997) also show ear differences. Khalfa et al. (1997) showed higher amplitudes of TEOAEs in right ears. Khalfa et al. (1997) showed right ears to have more significant tone decay and for left

ears to show a higher temporary threshold shift. The right medial olivocochlear system also shows significantly higher activity (Khalfa & Collet, 1996).

This right ear advantage thus may explain differences in the symmetry of ototoxic hearing loss, where the left ear displays more hearing loss than the right ear. Yet the differences observed in the aminoglycoside studies were more than 2-4 dB as proposed by McFadden (1993).

Further, possible asymmetry with ototoxicity from cisplatin has been observed in the study by Schmidt et al. (2008). They investigated the possibility of the right ear advantage in children undergoing chemotherapy (cisplatin). The study included 55 children and found that the left ear was slightly more affected in the range of 2-8 kHz to 8 kHz. The difference was significant at 4, 6 and 8 kHz. McFadden (1993) concludes that it is possible that the asymmetry in the efferent system may be related to the well-known cortical asymmetries that are believed to underlie speech perception, speech production, and other human abilities. This study shows that contrary to other literature, the cisplatin-induced hearing loss is not necessarily symmetrical. Additionally, asymmetrical or unilateral hearing loss in the case of cancer is often a result of tumour location or surgical or radiotherapeutic intervention (Schmidt et al., 2008). There is only limited evidence of asymmetric hearing loss, such as a case with initially bilateral, symmetric hearing loss after aminoglycoside therapy, in which the right ear recovered although the left ear remained hearing impaired (Moffat & Ramsden, 1977).

Another study by Huizing and de Groot (1987) mentioned that aminoglycoside induced hearing loss is not necessarily symmetrical. This study, however, occurred in 1987 and did not explicitly describe reasoning for this. Most studies appear to describe hearing loss resulting from ototoxicity as symmetrical; however, vestibular disturbances are described more often as asymmetrical (Waterston & Halmagyi, 1998; Elidan, Lin & Honrubia, 1987).

It appears that many studies are reporting high frequency and mostly bilateral hearing loss. Also, the degree of the hearing loss varies. In many instances, unilateral components have been reported, indicating asymmetry. Although some possible ideas have been presented to explain this, there is no conclusive evidence as to why these unilateral hearing losses are occurring.

4.6. Impact of Ototoxic Induced Hearing Loss on Quality of Life

Hearing loss can affect an individual's quality of life, due to impact on one communication.

In 2001, the WHO endorsed the International Classification of Functioning, Disability, and Health (ICF). This model can be displayed according to the figure below, as seen in the article by McDougall, Wright, and Rosenbaum (2010). This concept provides a framework for understanding functioning and disability whereas functioning encompasses all body functions and structures, activities, and participation, while the disability is an overarching term for impairments, activity limitations and participation restrictions. A person's functioning and disability are considered to arise from the interaction among health conditions, environmental factors, such as accessibility of the environments, peer relationships, service availability etc. and personal factors, such as age, gender, values, lifestyle, etc. (McDougall et al., 2010). Figure 4.2 depicts all these interactions which affect functioning and disability.

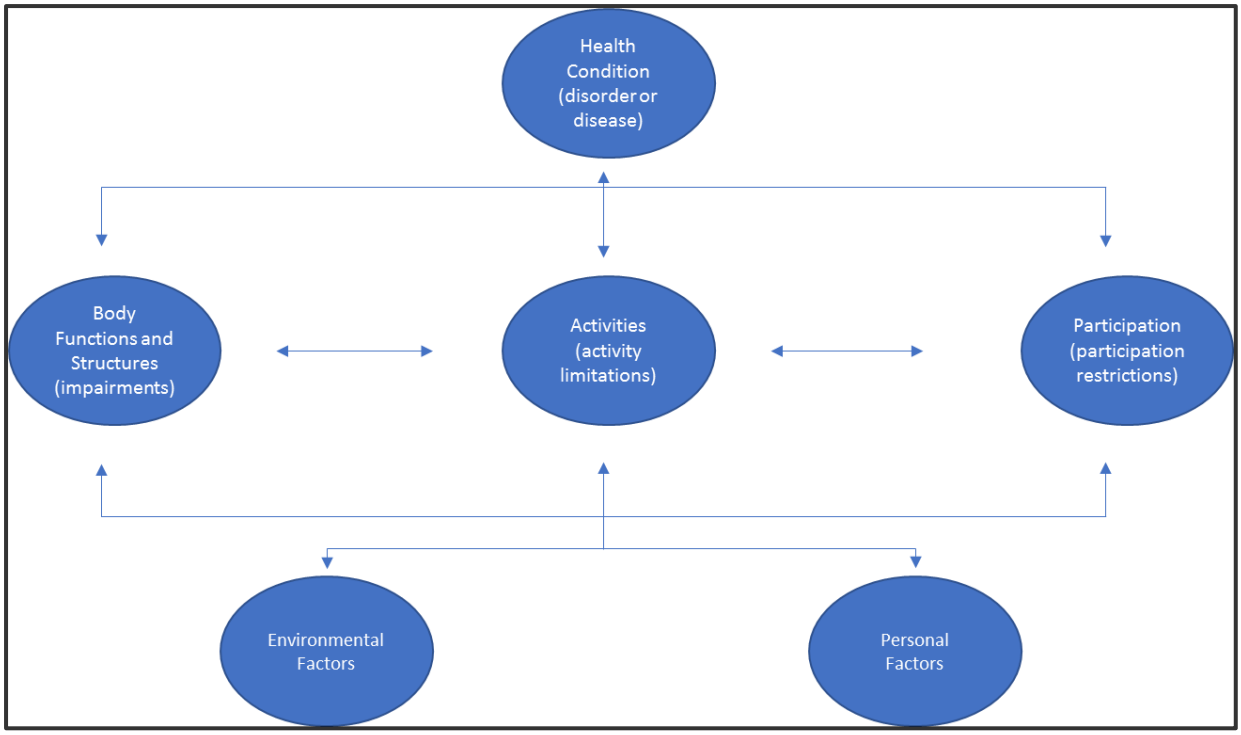

Figure 4.2. The World Health Organisation's model of functioning and disability (McDougall et al., 2010)

Burden of disease may be quantified with quality-adjusted life years (QALY) or DALYs. These both quantify the number of years lost due to a specific disease. The foundation for the QALY calculation is based on a multi-attribute theory where the following conditions are considered: utility independence between life years and health status, constant proportional trade-off and risk neutrality on life years. The QALYs are used in many costs analysis situations and can be a productive part of a decision-making process. Zeckhauser and Shepard (1976) first used the term 'quality-adjusted life year' to indicate a health outcome measurement unit that combines duration and quality of life. The QALY primarily calculates life expectancy based on the health-related quality of life, although it is not as simple (Sassi, 2006).

The QALYs provide a framework for the development of the DALY which is primarily a measure of disease burden as it weights the disability to the loss of functioning. The DALY considers age, the origin of disability as well as the quality of life weights

differently as to with the QALY. Both these measures are calculations to assess the outcomes (Sassi, 2006). The WHO assesses Burden of Disease using the DALYs as it is a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. The DALY metric assesses the burden of disease consistently across diseases, risk factors, and region (WHO, 2016c). Although these calculations are not being utilised in this research study, it highlights important aspects to consider when assessing the quality of life, and the effect that hearing loss can have on ones functioning and disability.

The potential disability of hearing loss from an already disabling disease such as TB highlights the disability aspect of the ICF where activity and overall functioning is affected. The effect of hearing loss or deafness can in-turn affect all spheres of a person's life, including socialisation, employment, and occupational aspects, emotional and self-esteem and overall and general wellbeing (Peterson & Rogers, 2015). A survey, conducted in the USA, found that 36% of individuals with hearing difficulty were unemployed in comparison to an unemployment rate of 25% for individuals with no disability (Ruben, 2000). The WHO estimated that 360 million people (over 5% of the world's population) are living with disabling hearing loss. Disabling hearing loss is distributed unequally across the world, with the highest burden living in low and middle-income countries (WHO, 2017). Even more so, TB is viewed as a disability in itself as South Africa will now provide disability grants for patients with TB (Green, 2015). The emotional aspects of hearing loss, which can also include anxiety, lack of self-confidence, depression and/or social isolation (Peterson & Rogers, 2015), combined with the stigma, depression, and anxiety from TB (Aydin & Ulusahin, 2001) places a 'double disability' on these individuals. Also, the current production of hearing aids meets less than 10% of the global need, and less than 3% in developing countries (WHO, 2017). Hearing loss can have a major impact on the ability of affected

individuals to secure jobs (Kidd, Sloane & Ferko, 2000) and, since most of TB patients are from poor socio-economic backgrounds (Lawn, Bekker, Middelkoop, Myer & Wood 2006), there will be increased demands on the country's social welfare and health budgets. There are currently demands on the budget as TB patients apply for social grants while they are sick. Yet, when they are physically well, they often need to apply for further disability grants resulting from their hearing loss.

The identification of the extent and pattern of hearing loss in the DR-TB population is essential to evaluate the QALY and DALY, but also to improve functioning and lessen this ‘double disability’.

4.7. Ototoxicity Monitoring

Objective and subjective monitoring of cochlear and vestibular function can help identify the toxic effect of the medication (Schellack & Naude, 2013). Monitoring for ototoxicity allows for the early detection of audiologic changes in order to permit the consideration of changes or alternative treatment regimen, as well as to allow for intervention once hearing handicap has occurred (Durrant et al., 2009; ASHA, 1994; Schellack & Naude, 2013).

The changes in treatment can comprise of a reduction in the dosage, a change in the timing of the dosage schedule, a temporary discontinuation of therapy so that the ear can "rest" and/or a switch to a less ototoxic drug (Vasquez & Mattucci, 2003; Durrant et al., 2009). In some cases, however, the physician will not be able to change the drug regimen because of the intensity or severity of the patient's illness (Vasquez & Mattucci, 2003). According to the NDoH Guidelines in 2015, suggestions to stop the drug, reduce the dose or increase the length of the dosing interval is recommended upon the detection of ototoxicity. However, it further mentioned that there is no evidence from randomised controlled trials to

support any of these interventions (NDoH, 2015). Nevertheless, changes in medication often occur in practice and are reported anecdotally by clinicians/audiologists to reduce the ototoxicity.

Furthermore, intervention allows the patients and/or the family to maintain effective communication should the hearing loss worsen, in cases when alternative treatment may not be a suitable or viable option (Durrant et al., 2009). When ototoxicity occurs, referral for vestibular and/or aural rehabilitation is indicated, particularly for patients who experience permanent hearing loss (Vasquez & Mattucci, 2003). Intervention for this hearing loss can include counselling (Konrad-Martin et al., 2005), hearing aid fitting (NDoH, 2015), implementation of communication strategies (Konrad-Martin et al., 2005), and in some cases, cochlear implants (Nichani et al., 2013).

4.7.1. Ototoxicity Monitoring Guidelines

There are three primary audiological methods to ototoxicity monitoring that have been dominant over the past few decades. These dominant trends include the basic audiologic assessment, high-frequency audiometry (HFA), and otoacoustic emission (OAE) measurement. These three methods vary in utility, reliability, purpose and applicability to different populations (Durrant et al., 2009).

Other measures mentioned by Durrant et al. (2009) include auditory evoked potentials such as high-frequency Auditory Brain Stem Responses (ABRs) or Auditory Steady-State Evoked Response (ASSR). While these electrophysiological measures may show overall technical efficacy, the results for high-frequency measurements are not as encouraging due to a considerably reduced dynamic range, another major challenge (in addition to the issue of standing waves) in all areas of high-frequency testing. These measures may, however, be useful in a paediatric population who may not be able to respond behaviourally with

traditional HFA (Durrant et al., 2009). However, as sedation may be needed, this may not be advisable because of sedation relation complications (Tobias & Leder, 2011).

Currently, there are very few guidelines published internationally recommending a monitoring protocol for ototoxicity. Various individual studies have proposed ideas. However, the existing guidelines available have been issued from ASHA (1994) and the American Academy of Audiology by Durrant et al. (2009). In 2015, the South African NDoH issued a recommended monitoring protocol for patients with DR-TB. They were adapted from the ASHA guidelines and recommend grading.

4.7.1.1. South African guidelines.

Despite the availability of a South African policy for monitoring ototoxicity (NDoH, 2015), research has shown that various hospital in South Africa follows their own protocols (Khoza-Shangase & Stirk, 2016). It was found that some hospitals in South Africa have implemented their own programs for monitoring ototoxicity from TB treatment, and there was no clear standard for managing the detected ototoxicity. They suggested that a monitoring program with an intervention method needs to be established in South Africa (Khoza-Shangase & Stirk, 2016).

4.7.2. Assessment of Ototoxicity

The Guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy developed by the ASHA Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulotoxic Drug Therapy and adopted by the ASHA Legislative Council (LC 36-93) in November 1993. This document discusses the role of the audiologists, various ototoxic drugs, the incidence of cochleotoxicity, basic principles of cochleotoxicity monitoring, procedures of cochleotoxicity monitoring, responsive/limited responsiveness and unresponsive patients, testing environments, children and aural rehabilitation. This document states it is the audiologists'

responsibility to identify at-risk patients and design and implement a suitable ototoxicity monitoring protocol, as well as the implementation of rehabilitative procedures (ASHA, 1994). In South Africa, the doctors and nurses are also responsible for identifying patients, and many nurses conduct testing due to the limited availability of audiologists.

Furthermore, this article (ASHA, 1994) mentions that the relationship between cochleotoxicity and drug administration parameters such as dosage, duration of treatment, and serum concentration is highly variable, and so dependence of sole reliance on dosage or serum concentrations is not reliable. The authors mention that the available evidence indicates that high-frequency audiometry is the method of choice for the earliest detection of ototoxic hearing loss. A monitoring protocol includes patient identification (those patients at risk and taking ototoxic medication), pre-treatment counselling, and baseline testing (for kanamycin it is suggested that baseline is indicted within 72 hours of the first dose administration (ASHA, 1994) as ototoxicity can occur after only a single dose (Vasquez & Mattucci, 2003). Subsequently, the recommendation for monitoring and follow-up tests at intervals that would allow the detection of the earliest signs of ototoxicity (ASHA, 1994). The South African guidelines recommend baseline measures within the first seven days of treatment, and subsequently weekly testing where possible, else monthly. In the continuation phase, three monthly testing is recommended for a total of six months (NDoH, 2015).

An outline of assessment and monitoring procedures, including the identification of risk factors and counselling, followed by audiological tests that can include the primary test battery, ultra-high frequency PTA and OAEs are detailed below. In addition, the timing of the testing should be considered in different populations and with different ototoxic drugs.

4.7.2.1. Identification of risk factors.

It is advised that risk factors develop ototoxicity be identified (Vasquez & Mattucci, 2003). These risk factors include previous use of an ototoxic agent, simultaneous exposure to

multiple ototoxic agents, administration of an ototoxic agent for more than 14 days, administration of multiple courses of an ototoxic drug, administration of an aminoglycoside in combination with a loop diuretic, high serum levels of an ototoxic agent (a consequence of a failure to monitor peak and trough levels), pre-existing sensorineural hearing loss with evidence of outer-hair-cell loss, impaired renal function and compromised hepatic function, age and individual genetic factors (Vasquez & Mattucci, 2003). Konrad-Martin et al. (2005) also mention poor general medical condition and reduced renal function as risk factors. A high temperature and duration of drug therapy can also be regarded as risk factors (Moore et al., 1984). Further aspects should be noted including ototoxicity occurring in patients who take an appropriate dose and in those who have average peak and trough levels.

The identification of all risk factors would be ideal, however, sometimes may not be possible. Genetic testing is extremely expensive, and identification of all the risk factors is not always possible, especially in South Africa, where the tester may not speak the language of the patient. Also, the patient may be unaware of his/her history. Therefore, even though risk factor identification would be an added benefit; the absence of risk factors cannot exclude a patient from ototoxicity monitoring.

4.7.2.2. Pre-treatment counselling.

Prior to the initiation of ototoxic treatment, patients should have counselling regarding the potential effects of the drugs on the auditory system. The medical doctor should include the risks and benefits of drug therapy, and the audiologist should counsel patients on signs and symptoms of cochlear damage and potential effects on communication ability (ASHA, 1994). The audiologist can further counsel patients and their families concerning ototoxicity-induced hearing loss, tinnitus, and dizziness, communication strategies, and the synergistic effects of noise and ototoxic damage (Konrad-Martin et al., 2005).

As patients have a right to information about their condition and the treatment options available, it is crucial to meet language and communication needs, and thus, due to the multitude of languages in South Africa, interpreters may be necessary (Health Professions Council of South Africa [HPCSA], 2008).

4.7.2.3. Basic audiological assessment.

The traditional necessary audiological test battery includes otoscopy, tympanometry, PTA (PTA), including air and bone conduction, and speech audiometry (Durrant et al., 2009).

Baseline evaluations are imperative for ototoxicity monitoring. This allows one to consider possible pre-existing hearing loss that may not be a result of the current ototoxic regimen. It thus allows for a clear basis for interpretation. Ideally, this should take place before the administration of the initial dose of the ototoxic regimen (Durrant et al., 2009, ASHA, 1994). Ideally, this baseline evaluation should include all tests that may be needed in subsequent testing, even if only a few are utilised for the follow-up monitoring. This is because, if a change does subsequently occur on the follow-up testing, more extensive testing will be needed at that time to determine if the change is secondary to the drug, or other factors, such as otitis media. A comprehensive basis will assist in preventing ambiguity with analysis of the results. The baseline tests should be as comprehensive as possible which can include PTA (up to 8 kHz), tympanometry, ultra-high frequency audiometry (UHFA), OAEs and speech audiometry (Durrant et al., 2009).

Yet, the traditional necessary audiological test battery only includes otoscopy, tympanometry, PTA including air and bone conduction, and speech audiometry (Durrant et al., 2009). It does not include UHFA and OAEs. However, all these tests take significant time to administer and conduct and may not be feasible at every follow-up. The NDoH (2015) recommends otoscopy, tympanometry, PTA (UHF where possible) and OAEs. They do not include bone conduction or speech audiometry.

- **Otoscopy**: An otoscopic examination is performed to evaluate the state of the outer ear, and tympanic membrane for abnormalities and/or infection (Rappaport & Provencal, 2002). Otoscopy determines the condition of the external auditory meatus and tympanic membrane and to ensure that there are no obstructions in the external canal or conditions that could influence additional testing procedures.
- **Cerumen Management**: Impacted cerumen can affect the reliability of tympanometry, distortion product otoacoustic emissions (DPOAE), and PTA. Therefore, the removal of cerumen allows for a clear external auditory meatus to assist in ensuring further reliable audiometric measures.
- **Tympanometry:** Tympanometry evaluates middle ear status through the depiction of tympanic membrane motility as a function of variations in air pressure (Clark, Roeser & Mendrygal, 2007). This test serves as an invaluable evaluative tool representing middle ear functioning (Clark et al., 2007). Also, the presence of middle ear pathologies results in severely diminished OAEs, and more severe cases may also influence the results obtained with ABR testing (Swanepoel et al., 2007), thus affecting the reliability of the OAE measures and air conduction PTA measures. Tympanometry is essential in South Africa, precisely due to high rates of HIV co-infection in XR-TB settings. Chronic outer and middle ear infections are prevalent in this population which can complicate testing and interpretation (Seddon, Godfrey-Faussett, Jacobs et al., 2012).
- **Pure Tone Audiometry**: PTA assesses hearing sensitivity as a function of frequency (Bess & Humes, 2008). It is a psychophysical assessment of auditory sensitivity and provides insight into the integrity of the auditory system as well as information relating to the symmetry, laterality, degree, and configuration of a patient's hearing thresholds (Harrell, 2002). In this hearing test, a hearing threshold is obtained at various frequencies with a calibrated audiometer (Guthrie, 2008). The purpose of testing hearing this way is

to help aid in making decisions regarding both the type and the extent of a patient's hearing loss (Martin & Clark, 2003). For those who can cooperate and participate in testing, PTA in the currently preferred method to test hearing (Seddon et al., 2012). Pure tones are presented (air and/or bone conduction) via circumaural headphones, ear canal insert transducers, sound field arrays or an oscillating bone transducer positioned on the mastoid. Patients are aware and instructed to respond in a manner that is consistent and conducive to their physical ability (Guthrie, 2008). Bilateral testing takes place for a range of frequencies, and the minimum volume or amplitude is recorded when the patient responds. Frequencies above 2 kHz are considered high frequency (Seddon et al., 2012). The necessary procedure for threshold determination consists of (i) familiarisation with the test signal and (ii) threshold measurement. The procedure is the same regardless of frequency, an output transducer, or ear under test (ASHA, 2005). The purpose of testing hearing this way is to help aid in making decisions regarding both the type and the extent of a patient's hearing loss (Martin & Clark, 2003). There is controversy about the audiometric criteria for threshold shift, which frequencies should be tested and what step size should be used when evaluating ototoxicity. A study by Konrad-Martin et al. (2010) explored the evaluation of a significant threshold shift, and which octave steps should be tested (sixth, third or half-octave steps). They evaluated 78 ears of 41 participants on cisplatin in comparison to 53 ears of 28 hospitalised participants not receiving ototoxic antibiotics. They found that compared with the half octave step size that is utilised clinically, use of smaller frequency steps improved test performance for threshold shifts at ≥2 or ≥3 adjacent frequencies. Best overall test performance was achieved using a criterion cut from ≥10 dB threshold shift at ≥2 adjacent frequencies tested in sixth-octave steps. Best test performance for the half octave step size was achieved for shifts ≥15 dB at one or more frequencies. As there is currently no set criteria more monitoring ototoxicity

and the grading scales clearly have their limitations as noted above, it is a critical study to note when drawing up a protocol.

- **Speech Audiometry**: Speech audiometry assesses one's auditory ability using words, which are much more representative, when compared to pure tones, of everyday listening experiences than pure tones. Measuring the ability to perceive speech provides the audiologist with a clearer picture of ones' functional hearing ability (van Zyl, n.d).

For this current study, air conduction PTA was chosen without bone conduction and speech audiometry due to the time it takes to test, and the medical status the patients may have (Durrant et al., 2009).

Apart from the conventional means of conducting the basic test battery, other methods are being explored to conduct tests where audiologists may not be available. The study by Jacobs et al. (2012) introduces the idea of telehealth in ototoxicity monitoring. They describe a system, with ototoxicity identification (OtoID), that includes a portable audiometer with high-frequency test functionality that meets ANSI/ASA S3.6-2010 standards and is capable of reliably detecting ototoxicity relative to a baseline period using an automated test. The system includes a wireless cellular modem that is capable of notifying a remote healthcare professional in the event that a significant change in hearing has occurred in the patient. The system was evaluated within a sound-proof booth, a noisy hospital ward, and within patients' homes and results indicated that the OtoID system could be utilised by patients to efficiently monitor ototoxicity remotely, which can ultimately enable early detection of ototoxicity and potentially avoiding this hearing loss (Jacobs et al., 2012). There is increasing interest from academics and clinicians in harnessing smartphone applications as a means of delivering health intervention. Despite the growing availability of a range of health-related mobile applications on the market, academic research on the development and evaluation of such apps is in the relatively early stages (Dennison, Morrison, Conway & Yardley, 2013). As

many patients living in rural areas do not have access to audiologists, this could be an option to explore. However, mobile health and telehealth needs exploration with extreme caution. Currently, the NDoH has purchased portable automated audiometers for this population, and although an official study has not yet occurred, various issues and unreliable results are noted from personal communication with audiologists and nurses in the field. These issues include difficulties with insert earphone placement and with the automated instructions and protocol. Furthermore, technological difficulties have been reported upon via personal communication with nurses required to use this system. Also, the test has not been validated on the DR-TB population. Therefore, in conclusion, telehealth has an important place in a resource-limited country; however, it needs careful implementation and it needs to be executed in consultation with many professionals in the field. Those implementing the procedures also need adequate training; not only how to operate the equipment, but how to note patient factors and possible defaults in the results.

4.7.2.4. Ultra-High Frequency Audiometry.

As ototoxicity manifests, initially in the outer hair cells, ultra-high frequencies are affected first. The ASHA guidelines for ototoxicity monitoring emphasise the increased test sensitivity achieved using ultra-high-frequency monitoring to detect ototoxicity (Konrad-Martin et al., 2005). UHFA comprises of air-conduction threshold testing for the frequencies above 8 kHz, ranging up to 16 or 20 kHz (Durrant et al., 2009).

UHFA allows for the detection of changes well before it becomes evident in the speech-related frequencies. This allows for a possible change in the drug therapy before a hearing handicap is evident (Durrant et al., 2009). However, there are limitations to UHFA as it may not always be suitable, especially for patients with the pre-existing hearing loss. Test-retest differences for ultra-high-frequency thresholds using modern equipment are generally reported being within ±10 dB for frequencies between 9 and 14 kHz (Konrad-Martin et al.,

2005). ASHA (1994) state that for patients with limited responsiveness, testing can be shortened, by reducing the frequencies tested but the high frequencies should be a priority.

The specific frequencies with the most sensitivity for ototoxicity monitoring (with aminoglycosides and cisplatin) were investigated. The frequencies that showed the most significant sensitivity was 8, 9, 10, 11.2 and 12.5 kHz (generally separated by 1/6 octave) (Fausti et al., 1999).

PTA is not performed routinely at above 8 kHz as frequencies in this range do not involve speech sounds (0.25kHz to 6/8kHz). Although in a study by Al-Malky et al., (2014) that was conducted in paediatric patients, it displayed that UHFA can detect ototoxic hearing loss more than standard PTA (Al-Malky et al., 2014). Yet PTA normative values for frequencies above 8 kHz are not yet established clearly (de Sá et al., 2007). Despite this, they are still useful for audiological monitoring of ototoxicity. By detecting a change in frequencies above 8 kHz, ototoxicity can be identified before it involves speech frequencies and affects communication (Singh, Saxena & Varshney, 2008).

4.7.2.5. Otoacoustic Emissions.

Otoacoustic emission testing is a recording of sounds generated within the cochlea (Prieve & Fitzgerald, 2002). OAEs are generally used as they can detect minor changes in cochlear function prior to changes in thresholds on either the conventional audiogram or UHFA (Guthrie, 2008). DPOAEs allow for information pertaining to the integrity of the cochlea to be obtained, therefore contributing to the differential diagnosis linked to auditory functioning at this level of the auditory system (Prieve & Fitzgerald, 2002). OAEs are physiological assessments of cochlear function and are extremely sensitive measures (Guthrie, 2008). As ototoxicity manifests in the outer hair cells initially (Durrant et al., 2009), it is a useful measure in patients receiving ototoxic medication. OAEs are classified according to the stimulus that elicits the emission, namely spontaneous and evoked OAEs

(Hall, 2000). In this assessment, coherent acoustic reflections and acoustic distortion products are measured in the external auditory meatus. These acoustic occurrences are obtained by specific stimulus frequencies or bandwidths via a transducer positioned close to the tympanic membrane and acoustically coupled to the external auditory meatus. The emissions generated are dependent on the homeostasis of outer hair cells electromechanical and mechanoelectrical transduction processes (Guthrie, 2008). The mechanoelectrical process involves the OAEs arising from a nonlinear electromechanical distortion within the human cochlear. This distortion is turn creates a source of energy in the outer ear which is then measured as the emission (Gorga et al., 1997).

Evoked OAEs require a stimulus, while spontaneous OAEs require no such stimulus. Spontaneous OAEs have little clinical value (Hall, 2000). Evoked OAEs includes into three types, namely TEOAEs, Stimulus Frequency OAEs (SFOAEs) and DPOAEs. These types require different stimuli to elicit the emissions, being a click stimulus, a continuous pure tone stimulus and two pure tones as the stimulus respectively (Martin, Jassir, Stagner, Whitehead & Lonsbury-Martin, 1998). TEOAEs and DPOAEs, however, remain the most useful in clinical practice. The presence of OAEs with normal middle ear functioning implies hearing within reasonable limits, while the reduction or absence of OAEs indicates reduced outer hair cell functioning and thus implies hearing loss. TEOAEs have been shown to measure a hearing loss up to 30 dB, yet when the hearing loss is greater, the TEOAEs are shown to be absent. DPOAEs, in contrast, the measure can still be measured when a hearing loss is between 50-70 dBHL (Gorga et al., 1997). As hearing loss resulting from ototoxicity may result in a moderate-severe or severe hearing loss (Sagwa et al., 2015), DPOAEs are likely more useful for this population.

Also, despite the clinical utility of behavioural hearing thresholds being primarily explored, it is well established that these measures are influenced by factors such as attention,

motivation, and patient compliance. Objective measures, such as DPOAEs, show clinical relevance and may be one of the only other practical ways to evaluate children and adults unable to respond behaviuorally. DPOAEs are a convenient and non-invasive means to detect an ototoxic change in outer hair cell function, which is the area affected explicitly by initial ototoxicity. Distortion generated in the cochlea in response to the two simultaneous pure tones ($f1$ and $f2$, $f1<f2$) can be recorded in the ear canal at frequencies mathematically linked to the stimulus frequencies. The most comprehensively studied and clinically used is the DPOAE at the frequency $2f1\text{-}f2$. Compared to normal-hearing ears, DPOAE levels are reduced with mild to moderate hearing losses and are rarely present when hearing thresholds exceed 60 dB HL (Poling, Lee, Siegel & Dahr et al., 2012).

Gender has shown to impact DPOAEs where females tend to have larger emissions when elicited with a low-frequency stimulus (Dunckley & Dreisbach, 2004), while males lose more DPOAE amplitude with a hearing loss that is proportional in females (Cilento, Norton & Gates, 2003). Age also shows the impact on DPOAEs; as age increases, DPOAE amplitudes decreases (Dorn, Piskorski, Keefe, Neely & Gorga, 1998). Ethnicity has shown to impact of TEOAEs, yet not on DPOAEs (Hall, 2000).

Interpretation of DPOAEs relies on a few factors, such as low environmental ambient noise levels, repeated replicated reading that confirms the results and the assurance of no middle ear pathologies that could affect the readings (Hall, 2000). The ambient noise level in the DPOAE is regarded at the noise floor, whereas the Declustering Potential is the emission level. The signal to noise ratio is the difference between the noise floor and Declustering Potential, and acceptance of the response is dependent on this (Hall, 2000). The ratio of 10 dB sound pressure level (SPL) or greater is accepted widely, as this is a clear indication of a cochlear response and that ambient noise levels have not interfered in the reading. However,

other studies have shown a 6 dB SPL, or even 3 dB SPL signal to noise ratio is acceptable (Chan, Wong & McPherson, 2004).

Determining effective ototoxicity detection and monitoring strategies using objective measures such as DPOAEs is an active area of research. However, there currently are no accepted protocols or criteria for ototoxic change using DPOAEs (Durrant et al., 2009). Most reports in patients receiving ototoxic drugs which have utilised objective measures such as DPOAEs, in which sensitivity was defined as a clinically significant change in the value of the objective measure (Konrad-Martin et al., 2005). Stavroulaki et al. (2002) reported that a significant change could be 2.4 dB. Cunningham (2011) however discusses that from clinical experience changes of 3-6 dB SPL from one test session to the next (while all other test parameters are held constant, or an attempt at that occurs) are accepted as significant and indicate a change in cochlear function. Opinions vary, and there are no agreed-upon decisions of a universal dB SPL amount that indicates a "significant change" from one test session to the next (Cunningham, 2011).

Therefore, for this current study, a clinically significant change attributed to ototoxicity is defined 6 dB or more at or above 2 kHz at one or more frequency unilaterally or bilaterally. A clinically significant change can be classified as 6 dB sound pressure level (SPL) or higher, as adapted from Cunningham (2011). Therefore, variability in detection threshold or standard deviation is from 0 to 5 dB SPL (Roede, Harris, Probst & Xu, 1993). The grading systems below also only take PTA into account, and no grading system has been developed to grade OAEs.

Screening with DPOAEs may be enhanced by testing only in the 3- to the 5.2-kHz range, thus decreasing testing time. Higher time averages to increase the signal-to-noise ratio and use of this narrower bandwidth might also allow for accurate bedside testing (Ress et al.,

1999). There are thus various considerations to consider when monitoring ototoxicity; including the population under investigation and resources available.

Both PTA (including UHFA) and DPOAE measures can complement each other. PTA is a psycho-physical measurement of hearing with the aim of getting complete knowledge of an individual's ability to interpret various kinds of acoustic stimuli (Huizing, 1951), whereas DPOAE have higher sensitivity than PTA in the monitoring of cochlear function (Sakashita et al., 1998), but not interpretation. OAEs can detect minor changes accounting from ototoxicity before they are evident on the audiogram (Guthrie, 2008). As DPOAEs do not require an individual to respond physically, this can occur when patients are too weak to participate in PTA. PTA is measured by placing earphones on an individual while the clinician presents different pure tones with various frequencies to each ear via the earphones. Whereas, with DPOAEs, the clinician places a probe in an individual's ear. This probe emits the stimulus of two 'primary tones' that vary in frequency, and the cochlea responds by producing sounds. The microphone then picks these miniature sounds/emissions on the probe, and this is a measurement of cochlear functioning, and not hearing, as hearing extends beyond the cochlea to the temporal lobe (Martin & Clark, 2003). Therefore, this study utilised both DPOAEs, PTA, and UHFA to allow for a comprehensive overview of the participants audiological functioning.

Despite the beneficial clinical utility of these DPOAEs, the correlation between DPOAEs and audiometric thresholds has been a topic of investigation. Varying degrees of correlation has been observed when comparing DPOAE to PTA as well as UHFA. These investigations are important as they allow the determination whether PTA, UHFA as well as DPOAEs need to be conducted, or whether the DPOAEs can be conducted instead of PTA of UHFA to save time.

Correlation was noted between DPOAEs (up to 8 kHz) and UHFA (up to 20 kHz) when used to detect ototoxicity in cisplatin patients. Results showed that they both detected the same ototoxicity; five of the ten patients (Yu et al., 2014). Correlation was further noted between DPOAEs and PTA in individuals with normal hearing (2 to 6 kHz). Moreover, extended high frequency (EHF) PTA (PTA) (up to 20 kHz) and DPOAEs (up to 8 kHz) were compared in patients receiving cisplatin. Although both EHF-PTA and DPOAE showed the same sensitivity in detecting ototoxicity, they did not produce the same results in all patients, and so perhaps the two tests can complement each other, not outweigh each other (Yu et al., 2014). A positive correlation was further noted in ordinary hearing persons between PTA and DPOAE at 2, 3, 4, 6 kHz (Campos & Carvalho, 2011).

However, weak correlation between DPOAEs and PTA was observed in the industrial setting. This study stated that there is no relevant predictive relationship between DPOAEs and PTA to monitor noise-induced hearing loss (Wooles, Mulheran, Bray, Brewster & Banerjee, 2015). Also, DPOAEs were shown to detect more hearing loss than PTA at 8.9,10 kHz (Daud, Mohamadi, Haron & Rahman, 2014), showing a reduced correlation between DPOAEs and UHFA.

In summary, both DPOAEs and PTA, specifically UHFA have a place in ototoxicity monitoring. Although there is a correspondence between the DPOAEs and PTA; the relationship is not always consistent. This translates into the need for both DPOAEs and PTA, specifically UHFA to complement each other, instead of their use in isolation.

4.7.2.6. Other tests to consider.

In addition to the possible inclusion of auditory evoked potentials such as high-frequency ABRs or ASSR (Durrant et al., 2009), other areas of the auditory system may also need further consideration. These could include the assessment of the vestibular system

(Walther, Hülse, Lauer & Wenzel, 2015), as well as the evaluation of tinnitus (Konrad-Martin, Reavis, McMillan & Dille, 2014).

A comprehensive monitoring program was developed for veterans undergoing chemotherapy. This program recommends the screening for tinnitus as well as patient education about ototoxic hearing loss and tinnitus. The Tinnitus Monitoring overview (TOMI) is mentioned as a clinical tool to detect tinnitus onset or tinnitus changes in the tinnitus perception during treatment. An ototoxicity risk assessment is also recommended to allow for an individualised treatment profile (Konrad-Martin et al., 2014).

Also, not only is hearing assessment advised for some ototoxic agents, but vestibular damage may also occur. Walther et al. (2015) suggest that for diagnosis of suspected vestibulotoxic effects, the video head impulse test and vestibular evoked myogenic potentials seem to be suitable procedures for objective assessment. Yet kanamycin and capreomycin appear to be more ototoxic whereas some drugs are more vestibulotoxic.

4.7.2.7. Timing of testing.

The monitoring of hearing levels should regularly be monitored. The timing of monitoring tests is recommended as per Figure 4.3.

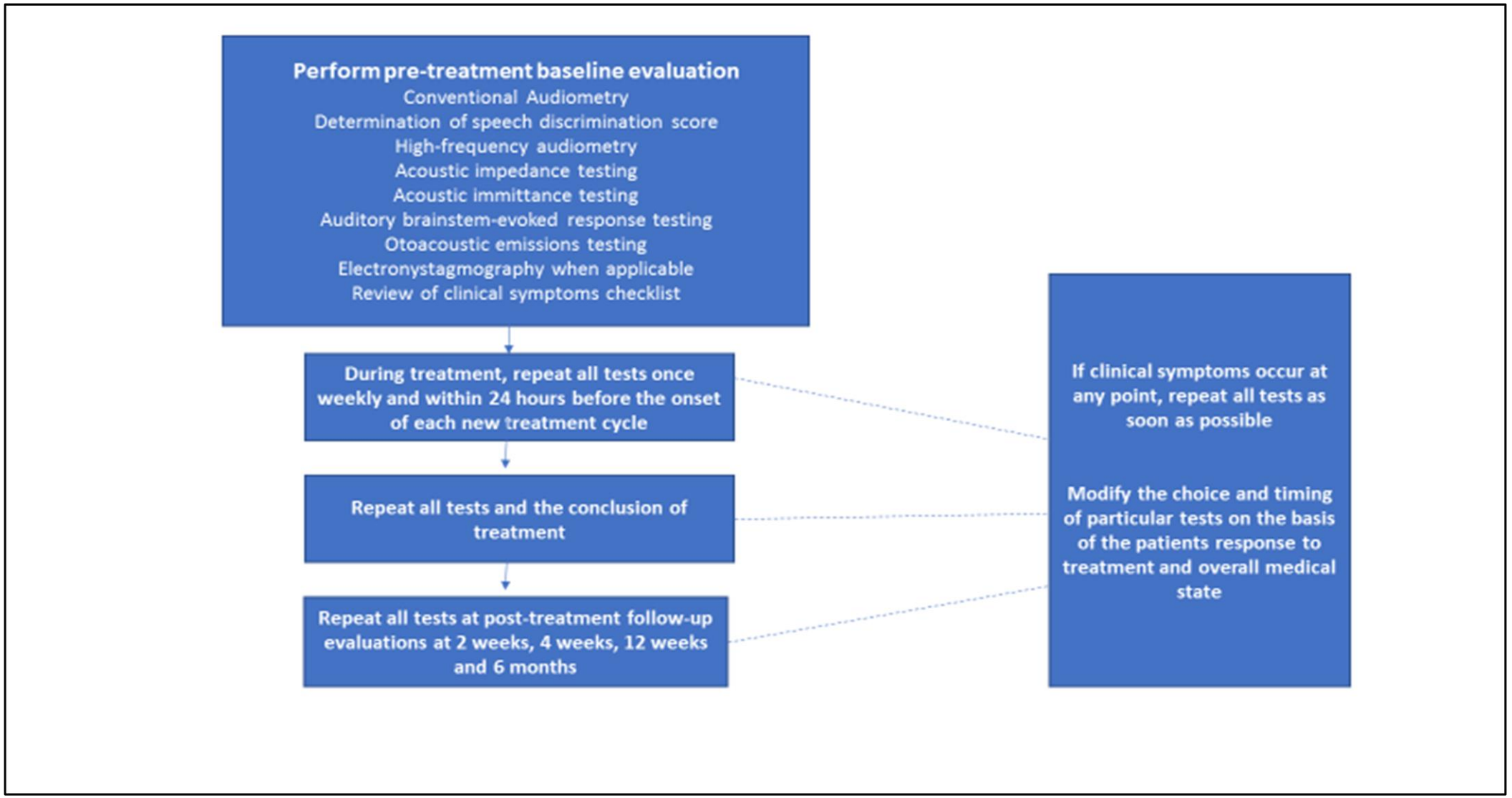

Figure 4.3 Monitoring Protocol for patients who are undergoing treatment with a potentially ototoxic drug (Vasquez & Mattucci, 2003)

ASHA (1994) discuss that patients receiving antibiotics should have a weekly evaluation and the frequency of monitoring should be increased or decreased depending on the changes observed. If a decrease in hearing is noted, the patient should be retested within 24 hours to confirm the damage, and the physician should be informed as soon as possible of a validated change. Also, patients who complain of symptoms consistent with cochlear or vestibular damage must be seen immediately by the audiologist. This basic monitoring plan can evolve to be more sensitive if the time and personnel are available. A more stringent plan includes monitoring every two to three days for patients receiving aminoglycosides, which could result in earlier identification of ototoxicity (ASHA, 1994).

In contrast, weekly to fortnightly audiograms are recommended after baseline evaluation, though financial and logistical barriers can limit this (Duggal & Sarker, 2007). From ASHA (1994), Duggal and Sarkar (2007) and Vasquez and Mattucci (2003), monitoring is recommended from every two to three days to fortnightly. This protocol needs also to consider the feasibility of patients attending the follow-up monitoring and may need adjustment based on the specific population and resources. Counselling is not noted typically as a monitoring procedure, yet as ototoxicity monitoring is to allow for opportunities for counselling (Konrad-Martin et al., 2005), implementation of the counselling should be in conjunction with the serial audiometric tests.

The NDoH recommends testing as adapted from ASHA (1994), however, with a few changes. They recommend baseline testing, ideally prior to administration of the ototoxic drug, and if this is not possible, they recommend baseline testing within the first seven days of treatment. Subsequently, as per ASHA, they recommend weekly tests (ASHA, 1994), yet if this is not possible, monthly testing is recommended, and in the continuation phase of DR-TB treatment, testing every three months is recommended for six months in total. This

continuation phase is from the time that the use of the injectable (aminoglycoside or capreomycin) until termination (NDoH, 2015).

The specific interval to initiate management and treatment is unclear. Vasquez and Mattucci (2003) discuss that referral for vestibular and/or aural rehabilitation is indicated when ototoxicity occurs. The NDoH (2015) guidelines discuss that should ototoxicity be detected; the drug could be stopped, dosage to be reduced, the length of the dosing interval to be increased or to retain current therapy while increasing the frequency of monitoring to identify further deterioration early. It then states that with the pre-existing hearing loss, the initiation of the patient onto bedaquiline or linezolid should occur, or if a change occurs, then the patient can be switched to these drugs (NDoH, 2015). The NDoH (2015) also suggest aural rehabilitation following the diagnosis of hearing loss. Therefore, counselling and communication strategies can begin to be implemented as part of management while monitoring is taking place. Counselling is often difficult due to language barriers, and interpreters may be needed (HPCSA, 2008). It is unclear when to consider hearing aid fitting; during treatment when hearing loss is detected, post-treatment, or six months post the termination of the aminoglycoside treatment. Also, in South Africa, hearing aids are often unavailable in the public sector, due to budget constraints, and availability of audiologists.

From observation and consultation with other audiologists, often, baseline testing is not conducted due to concern around the infectious nature of the patient. Also, patients often do not return consistently for their follow-up treatment and audiological monitoring due to transport and employment constraints. As per Konrad-Martin et al. (2005), monitoring is to allow counselling and implementation of aural rehabilitation (Konrad-Martin et al., 2005). Perhaps, should this be implemented, return for monitoring may be more successful.

Furthermore, the benefit of hearing aids is minimal to moderate (NDoH, 2015), and cochlear implantation is limited due to facilities available. In Gauteng Province, only two

state hospitals conduct cochlear implants (South African Cochlear Implant Group [SACIG], 2017).

4.7.2.8. Challenges with ototoxicity monitoring in South Africa.

The NDoH guidelines (2015) describe some critical factors, yet they are missing a few aspects that are important for the population as well as for the correct implementation of the guidelines. The guidelines do not discuss the type of OAE (DPOAE versus TEOAE) as well as the protocol of repeated measures, noise monitoring and the classification of a significant audiological shift with OAEs. It considered the ASHA criteria as a significant shift for PTA (NDoH, 2015) however, this is not necessarily ideal for the South African population, and do not guide the change in treatment.

There are also multiple challenges with monitoring ototoxicity in the South African population (and many other developing countries). Importantly, primary audiological equipment is often lacking, and so alternate ways of assessing hearing need further investigation. Ramma and Ibekwe (2012) investigated a self-report of auditory dysfunction questionnaire in adults with DR-TB (n = 53). The questionnaire was followed by an audiometric examination, including otoscopy, screening tympanometry, and PTA. They found self-report of hearing loss was a poor indication of auditory function in patients with a mild to moderate degree of hearing loss, yet it was good when the hearing loss was severe. Self-report is therefore unreliable, and it is essential for audiometric equipment to be available at DR-TB treatment centres (Ramma & Ibekwe, 2012). Yet, the NDoH (2015) recommends the use of the Hearing Handicap Inventory when equipment is not available. Although the guideline does note that it is only used once hearing loss has already developed, it does not discuss the degree of this hearing loss. As per Ramma and Ibekwe (2012), if it is used, it will only detect profound loss, and so the applicability is questioned.

Furthermore, as budget may be limited in South Africa, an ideal protocol may need adaptation to include fewer tests. However, equipment is vital to obtaining accurate and valid audiological monitoring, and a relevant and specific protocol needs to be drawn up for DR-TB patients within South Africa. These protocols, however, need additional development for the South African context, as the ASHA guidelines, provide useful information, do not take many South African specific contextual aspects into account. Unique monitoring protocols are relevant specific populations and vary according to the clinical purpose and practicalities available. For example, PTA may not be possible for extremely ill and non- or limited-responsive patients, where OAEs may be suitable as no behavioural response is required. On the other hand, OAEs do not always indicate hearing loss, but rather the loss of cochlear function. Also, HFA and OAEs may not be useful in patients with the pre-existing hearing loss, as they may already have absent OAEs and 'no response' at the high frequencies, and then the basic assessment in this case in more suitable (Durrant et al., 2009). Moreover, with any protocol chosen, infection control is essential to prevent the transmission of infection (Franklin & Grady, 2001), which is specifically relevant to this DR-TB population in South Africa.

4.7.3. Therapeutic Drug Monitoring

More recently there have been suggestions of TDM to prevent toxicity when using aminoglycosides (Harris & Heinze, 2015). The evidence for this is suggested in various studies (van Altena et al., 2017; Engler et al., 2015; Black et al., 1976). However, the exact recommendations for adjustments are not clear.

There is conflicting evidence regarding the effects of dosage adjustments to reduce ototoxicity (van Altena et al., 2017; Engler et al., 2015; Black et al.,1976; Ried, Horn & McKenna., 1990; Peloqion et al., 2004; Rybak et al., 1999; Avent et al., 2011). A recent study, published after this current study took place, indicated the correlation between TDM

and ototoxicity in the DR-TB population (van Altena et al., 2017). This study aimed to use TDM targeting to maintain efficacy while reducing ototoxicity. This study included 57 patients with MDR-TB or XDR-TB receiving amikacin or kanamycin as part of their TB treatment for at least three days. The results showed that the extent of hearing loss was limited and correlated with the cumulative drug dose per kg body weight during daily administration. At a median dose of 6.5 mg/kg, a correlation was found between the dose per kg bodyweight during daily dosing and the extent of hearing loss in dB at 8 kHz. This study suggested that the efficacy at this lower dosage is maintained with limited toxicity, however also suggested that further randomised controlled trials need to be conducted to provide more proof regarding safety and efficacy of TDM (van Altena et al., 2017).

Furthermore, the positive effect of TDM to reduce ototoxicity was noted in a neonatal study with amikacin (Engler et al., 2015). Correlations with high trough levels and ototoxicity were observed (Engler et al., 2015). Black et al. (1976) also showed the causative relationship between amikacin trough levels and ototoxicity. This study showed 57% of patients with a peak serum level exceeding 32 μg/ml, and 55% of patients with trough levels exceeding 10 μg/ml developed cochlear damage (Black et al., 1976). According to a study by Peloquin et al. (2004), the pharmacokinetics of streptomycin, kanamycin, and amikacin were nearly identical, and so this theory could potentially be transferred to kanamycin. Moreover, a meta-analysis, conducted by Ried, Horn and McKenna (1990), highlighted a study whereby patients who underwent TDM showed less ototoxicity compared to patients who were not monitored. These patients were taking theophylline or digoxin.

However, another study, however, showed that the trough levels of aminoglycosides (gentamicin, kanamycin, and streptomycin) were not associated with ototoxicity, yet duration of treatment and treated total dose received was associated with hearing loss (Peloquin et al., 2004). This study showed that the size of the dose (milligrams per kilogram), the frequency

of administration (daily or thrice-weekly), and the C_{max} did not predict ototoxicity. This study further detailed that the median C_{max} for ototoxic patients was 55 mg/ml (range, 32–113 mg/ml), and it was 53 mg/ml (range, 26–100 mg/ml) for nontoxic patient. All patients, but two patients had troughs of ‹2 mg/ml at 24 hours after dosing, and all had calculated troughs at 48 hours after dosing of 0 mg/ml. The streptomycin group had the lowest percentage of ototoxic patients (19%, compared with 42% of those receiving kanamycin and 55% of those receiving amikacin) (Peloquin et al., 2004). This study conflicts the above studies as the pharmacokinetics factors. Specifically, the trough levels were not associated with ototoxicity. The study above showed that the size of the dose, the frequency of the dose and C_{max} did not affect ototoxicity.

Though, in contrast to Peloqion et al. (2004), a study by Rybak et al. (1999) did show that the frequency of the dose can affect ototoxicity. This study included twice daily and once daily dosages of aminoglycosides. For the twice-daily dosing group, target peak concentrations in serum were 8 to 10 mg/litre for those with respiratory infections and 5 to 6 mg/litre for those with all other indications for gentamicin and tobramycin treatment, with trough concentrations of ‹2.0 mg/litre. For patients who received amikacin, peak concentrations in serum were 30 to 40 mg/litre for those with respiratory infections and 20 to 30 mg/litre for all other patients. Desired trough amikacin concentrations were ‹10.0 mg/litre. Target peak concentrations of gentamicin or tobramycin in serum concentrations for the once-daily dosing group were 16 to 20 mg/litre for those with respiratory infections and 10 to 12 mg/litre for patients with other infections. The desired peak serum amikacin concentrations were 60 to 80 mg/litre for patients with respiratory infections and 40 to 60 mg/litre for all others. The desired trough concentrations for once-daily dosing were targeted to be below one mg/litre. These target concentrations were based on doubling of the conventional target ranges for the Detroit Receiving Hospital and University Health Centre.

Initial dosing was based on population parameters in conjunction with the patient's calculated creatinine clearance and estimated ideal body weight. After obtaining serum aminoglycoside levels, dosing regimens were adjusted to maintain peak and trough concentrations in the targeted ranges. Trough concentrations (at 12 and 24 hours for groups who received aminoglycosides twice and once daily, respectively) were extrapolated by using a one-compartment equation with data for the serum samples obtained at the various times. Audiologic testing performed at the baseline (within 72 hours of the start of therapy), weekly thereafter or sooner if deemed clinically necessary, and after the cessation of therapy. Ototoxicity was defined as a decrease in the auditory threshold of at least 15 dB at two adjacent tested frequencies in one or both ears. Twenty-two patients, ten with twice-daily dosing and 12 with once-daily dosing, received two or more audiometric evaluations during and after treatment. Of these patients, one who received twice-daily aminoglycoside therapy met the criteria for ototoxicity. This study may show that twice daily dosing portrays a higher possibility for ototoxicity than once daily. However, the sample size was too small to make this correlation statistically. It is important to note, that as long as once-daily dosing of an aminoglycoside is at least as efficacious as conventional dosing, it may be beneficial to reduce toxicity (both ototoxicity and nephrotoxicity) (Rybak et al., 1999).

As, mycobacteria replicate at a significantly slower rate than other pathogenic bacteria, aminoglycoside treatment of these infections has traditionally been on a daily, three times per week, or even two times per week basis (Peloquin et al., 2004). Aminoglycosides may adversely affect auditory, vestibular, and renal function. It is unclear which parameter, if any, is most associated to the development of these toxicities, namely the peak serum concentration (C_{max}), the trough serum concentration, or the total milligrams per kilogram received (Peloquin et al., 2004).

Although these parameters are unclear, there has been some research displaying possible relationship, whether it be between trough levels and ototoxicity (van Altena et al., 2017; Engler et al., 2015) or between duration of treatment and total dose with ototoxicity (Peloqion et al., 2004), and/or between the frequency of dosing with ototoxicity (Rybak et al., 1999). Despite these possible relationships, there are currently no guidelines of pharmacokinetic modelling to reduce ototoxicity, specifically for kanamycin and capreomycin in the DR-TB population.

However, with a literature search, a few recommendations that have been proposed for pharmacokinetic modelling of aminoglycosides (Avent et al., 2011; Droege et al., 2016). As capreomycin is similar in structure to aminoglycosides, these recommendations could also apply.

Avent et al. (2011) mention there are two pharmacodynamic predictors of efficacy for aminoglycosides which are: the AUC: MIC and the C_{max}: MIC ratios. Dosing should thus aim to optimise these parameters. Target AUC values of 80 to 100 μg /ml and C_{max} 8 to 10, respectively are based on animal and human pharmacodynamic studies. The patients influence these parameters; as the C_{max}: MIC ratio is related almost exclusively to the volume of distribution, whereas the AUC: MIC ratio is influenced by both volume of distribution and clearance (Avent et al., 2011).

When patient individualisation dosing strategies are used based on the subject's weight and aimed at a therapeutic range to optimise clinical outcomes, a more significant percentage of patients will achieve the targeted concentration as compared with patients who receive a fixed dose strategy. Patients who attained targeted therapeutic serum concentrations of aminoglycosides early in their treatment course have shown an improved clinical outcome (Avent et al., 2011). Also, the frequency of pharmacokinetic monitoring depends on the

patients' clinical status, and there are no formal recommendations to date (Droege et al., 2016).

Several nomograms and algorithms have been developed to individualise pharmacokinetic monitoring for gentamicin. Three significant methods of dose individualisation commonly used to target specific pharmacokinetic parameters are (i) linear regression analysis (one compartment model), (ii) population methods and (iii) Bayesian estimation procedures. This standard can be extrapolated for kanamycin and capreomycin, as they are similar compounds (Avent et al., 2011). The skills of a clinical pharmacologist or clinical pharmacist are required for this type of ototoxicity monitoring and thus would form part of an ototoxicity monitoring team (Schellack & Naude, 2013).

Despite the use of aminoglycosides for decades, the ideal method of administration and the preferred dosing schemes for most of their therapeutic indications needs further enhancement. Individualized pharmacokinetic and pharmacodynamic monitoring has the potential of minimising toxicity and clinical failures of these agents. Also, many pharmacokinetic parameters of aminoglycosides have been obtained from healthy volunteers and not sick patients (Pagkalis, Mantadakis, Mavros, Ammari & Falagas, 2011).

Thus, the establishment of a pharmacokinetic model within the DR-TB population is imperative in order to allow for the monitoring and possible reduction of toxicity. Monitoring of blood concentrations of patients taking kanamycin and capreomycin may be greatly advantageous in the adjustment of the treatment which may influence ototoxicity. Aminoglycosides display concentration-dependent efficacy and toxicity, and thus these patients may benefit from pharmacokinetic modelling and subsequent therapeutic drug monitoring (Touw et al., 2009). Pharmacokinetic modelling and therapeutic drug monitoring are currently not recommended as part of the routine monitoring of ototoxicity for DR-TB. With more substantial evidence, it is possible that the monitoring of serum levels may be

included in the ototoxicity monitoring protocol. However, more research in this area is required and could be useful, specifically with kanamycin and capreomycin for DR-TB.

4.7.4. Grading Systems

For research studies or clinical application, a grading system is often used to describe the hearing loss as measured by air conduction PTA. Several systems have been developed, namely the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades (Fisher et al., 2004), TUNE (Theunissen et al., 2014), Brock's Hearing Loss Grades (Brock, Bellman, Yeomans, Pinkerton & Pritchard, 1991), Chang and Chinosornvatana (Chang & Chinosornvatana, 2010) as well as the SIOP Boston Ototoxicity Scale (Brock et al., 2012) (see Table 4.1). Although mainly designed for children, some have adult applications, such as the CTCAE scale, while the others, for example, the Brock and SIOP scales, do not. There has been a need identified for ototoxicity grading systems to allow clinicians to understand the severity of ototoxicity and standardised treatment based on the grades (Peterson & Rogers, 2015). These grading scales, such as the CTCAE (for adults and children), TUNE, Brock, Chang and Chinosornvatana and SIOP are described in Table 4.1.

Table 4.1

Ototoxicity Grading Scales according to NCI CTCAE and TUNE in adults and children

ADULT SCALES			
NCI CTCAE (Grades up to 8 kHz) (Durrant et al., 2009; (Fisher et al., 2004)		**TUNE** (Grades up to 12.5 kHz) (Theunissen et al., 2014)	
Originally developed for children yet has adult applications		Developed for Adults	
		Grade 0	No Hearing Loss
Grade 1	Threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more adjacent frequencies in at least one ear.	Grade 1a	Threshold shift ≥ 10 dB at [8-10-12.5] OR subjective complaints in the absence of a threshold shift
		Grade 1b	Threshold shift ≥ 10 dB at [1-2-4]
Grade 2	Threshold shift or loss of >25-90 dB, averaged at two adjacent test frequencies in at least one ear	Grade 2a	Threshold shift ≥ 20 dB at [8-10-12.5]
		Grade 2b	Threshold shift ≥ 20 dB at [1-2-4]
Grade 3	Hearing loss sufficient to indicate therapeutic intervention, including hearing aids. Adults: >25-90 dB, averaged at three adjacent test frequencies in at least one ear.	Grade 3	Hearing level ≥ 35 dB HL at [1-2-4] de novo
Grade 4	Indication for cochlear implant and requiring additional speech language-related services. For adults, a profound hearing loss is at >90 dB HL.	Grade 4	Hearing level ≥ 70 dB HL at [1-2-4] de novo

PAEDIATRIC SCALES	
Brock (1991) (Grades up to 8 kHz) (Brock et al., 2011)	**Chang and Chinosornvatana** (Grades up to 12 kHz) (Chang & Chinosornvatana, 2010)
Based on absolute hearing level rather than change from baseline and based on bilateral loss	Based on absolute hearing threshold levels and a modification to the Brock scale. It detects milder degrees of hearing loss (Bass et al., 2014).
Grade 0 < 40 dB at all frequencies	Grade 0 ≤ 20 dB at 1.2, and 4 kHz
Grade 1 ≥ 40 dB at 8 kHz only	Grade 1a ≥40 dB at any frequency 6 to 12 kHz Grade 1b >20 and < 40 dB at 4 kHz
Grade 2 ≥ 40 dB at 4 kHz and above	Grade 2a ≥40 dB at 4 kHz and above Grade 2b >20 and < 40 dB at any frequency below 4 kHz
Grade 3 ≥ 40 dB at 2 kHz and above	Grade 3 ≥40 dB at 2 or 3 kHz and above
Grade 4 ≥ 40 dB at 1 kHz and above	Grade 4 ≥40 dB at 1 kHz and above

SIOP (Grades up to 8 kHz) (Brock, et al., 2012)		**NCI CTCAE** (Grades up to 8 kHz) (Durrant et al., 2009)	
Modification of the Children's Hospital of Boston functional hearing loss scale, and based on hearing thresholds, and is sensitive to high-frequency hearing loss and mild degrees of impairment (Bass et al., 2014)		Based on loss from baseline and hearing thresholds	
Grade 0	≤20 dB HL at all frequencies		
Grade 1	>20 dB HL (i.e. 25 dB HL or greater) SNHL above 4 kHz (i.e. 6 or 8 kHz)	Grade 1	Threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more adjacent frequencies in at least one ear.
Grade 2	>20 dB HL SNHL at 4 kHz and above	Grade 2	Threshold shift or loss of >25-90 dB, averaged at two adjacent test frequencies in at least one ear
Grade 3	>20 dB HL SNHL at 2 kHz or 3 kHz and above	Grade 3	Hearing loss sufficient to indicate therapeutic intervention, including hearing aids.
Grade 4	>40 dB HL (i.e. 45 dB HL or more) SNHL at 2 kHz and above	Grade 4	Indication for cochlear implant and requiring additional speech language-related services.

Although not a grading scale, ASHA (1994) developed specific criteria to document change in hearing, which is beneficial for both high-frequency audiometry and the conventional audiometry. They, however, do not define the specific frequencies (Theunissen et al., 2014). These criteria describe significant ototoxic change when one of the following three criteria are met: (a) ≥20 dB decrease at any one test frequency, (b) ≥10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were obtained previously (Konrad-Martin et al., 2005).

The WHO also uses specific criteria to describe hearing loss which includes the use of a speech frequency pure tone average (average of hearing thresholds at 0.5, 1, 2, and 4 kHz). According to the WHO, hearing loss is described as a pure tone average of greater than 25 dB HL in both ears (Lin, Niparko & Ferriucci, 2011). The definition of hearing loss, however, is not necessarily useful for ototoxicity, as hearing loss may be unilateral as observed in various studies (Sharma et al., 2016; Javadi et al., 2011), as well as initiates in the high frequencies first (Harris & Heinze, 2015). The WHO criteria do not appear to be useful for early identification of ototoxicity.

While these grading scales have gone through various studies, none have been developed for patients with DR-TB, and no system is currently utilised in South Africa. It would be useful for medical doctors, nurses, pharmacists, and audiologists to understand the relevant grades of hearing loss and subsequent relative management to patients DR-TB medication regimen. Thus, the proposal of a new grading system in the DR-TB population is imperative to assist in management decisions for the treating clinicians.

Chapter 5: Methodology

This chapter describes the method implemented in this study. For the purposes of this study, it begins with the aims and objectives of the study. It progresses to explain the research design and research sites. Following this, the participants are described in detail, including the sample selection procedures and size. Subsequently, the data collection procedure is illustrated, which includes an overview, the personnel involved, the enrolment process, audiological and pharmacological measures and other measures and equipment involved in the data collection. The ethical considerations are discussed followed by the reliability and validity of the study. Lastly, the data management plan and statistical analysis and procedures are outlined.

5.1. Research aims

5.1.1. Main Aim

The main aim of this study was to determine the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship with hearing levels.

- The willingness of patients to participate in a pharmacokinetic study in conjunction with hearing evaluations.
- To investigate whether TDM could potentially be utilised in terms of dosage adjustments of kanamycin and capreomycin.

The following sub-aims and objectives are delineated in order to achieve the main aim:

5.1.2. Sub Aims

5.1.2.1. To determine the changes in hearing levels in patients undergoing treatment with kanamycin and capreomycin for DR-TB.

- To determine the prevalence of abnormal findings on baseline hearing assessments.
- To determine the change in hearing levels from baseline.

5.1.2.2. To investigate the kanamycin and capreomycin pharmacokinetics in patients undergoing treatment for DR-TB.

- To investigate the peak and trough levels of kanamycin and capreomycin at two weekly intervals for the first three months of treatment.
- To investigate the relationship between the kanamycin and capreomycin kinetics with creatinine levels.
- To examine the relationship between the pharmacokinetics/ pharmacodynamics of kanamycin and capreomycin to culture conversion after the three-month period.

5.1.2.3. Examine the relationship between kanamycin and capreomycin pharmacokinetics and hearing levels.

- To examine the relationship between kanamycin and capreomycin dosing and hearing levels throughout the three-month study period.
- To explore the relationship between kanamycin and capreomycin dosing and the progression of hearing loss.

5.2. Research Design

This study was conducted within a quantitative research paradigm. This feasibility study employed a prospective, exploratory, descriptive and case series research design that was also cross-sectional in nature.

Quantitative research refers to the traditional scientific approach to research, driven by systematic and methodological procedures which places value on objectivity, prediction, and control (Koch & Harrington, 1998; Streubert & Carpenter, 1999). The goal of this type of research is further described as to determine the relationship between an independent variable and a dependent or outcome variable within a population (Babbie, 2010). In this study, the independent variable was the pharmacokinetics of kanamycin and capreomycin with the dependent variable or outcome being the hearing levels. This study utilised objective and quantifiable methods of data collection, including the audiometric evaluations and pharmacokinetic measurements.

5.2.1. Feasibility

A feasibility study is, for the purpose of this current study, described according to the conceptual framework proposed by Eldridge et al. (2016) that specifically relates to the preparation for randomised control studies that evaluate the effect of an intervention. A feasibility study asks whether something can be carried out and if the researchers should proceed with the aim. If the answer is yes, then it addresses how this should transpire (Eldridge et al., 2016). Therefore, this study assessed the feasibility of investigating kanamycin and capreomycin pharmacokinetics in relation to the hearing levels (Eldridge et al., 2016).

5.2.2. Exploratory

Exploratory research is useful and appropriate for studies that are addressing a subject about which there are high levels of uncertainty and a relatively unfamiliar field (Mouton & Marais, 1990). These studies typically use a smaller sample size and explore unknown phenomena (Huttlinger, 2006).

This form of research is often conducted to determine the feasibility of or need for more extensive research or to establish some sort of baseline that could lay the groundwork of a future study (Huttlinger, 2006).

Exploratory research has a flexible design that enables the researcher to investigate and examine all aspects of the phenomenon being studied. It allows the researcher to explore all new emerging ideas, and change direction if needed. It often lacks formal structure (Huttlinger, 2006).

A critique of this design includes that these studies may be limited in scope and focus and may not be generalizable to a larger population and cannot be utilised as a basis for prediction. However, these studies are used to uncover or discover information about little-known concepts, to explore relationships between and among variables, to uncover more information about human behaviours in a naturalistic environment and to lay the groundwork for more systematic testing of hypotheses (Huttlinger, 2006).

This study was exploratory as the pharmacokinetics of kanamycin and capreomycin in patients with DR-TB had not been measured previously. Also, the investigation of the relationships between capreomycin and kanamycin with hearing levels was not investigated previously.

5.2.3. Descriptive research

Descriptive research, a level of quantitative research (Walker, 2005), provides an account of the characteristics of individuals, groups or situations (Jack & Clarke, 1998) that

may form the initial stage of more intricate designs. The overall aim is to discover new meanings, describe what currently exists and as well detail the frequency of occurrences and the categorisation of information (Walker, 2005). The purpose of these studies is to observe, describe and document aspects of a situation which may serve as a starting point for the conceptualisation of a further hypothesis. This study aimed to describe the pharmacokinetics of kanamycin and capreomycin in relation to the hearing levels. Descriptive designs, as such, have a crucial role to play in the development of new knowledge, generating questions and hypotheses that could form the basis of further research (Walker, 2005). The analysis of this study included the description of group differences, trends within the group, and relationships within the different variables (Gravetter & Forzano, 2011).

5.2.4. Prospective

This study was prospective in nature as it was carried out into the future, and could be tailored to collect specific exposure data (Levin, 2003). The protocol was developed, and subsequently, the data collected. Advantages can include the ability to gather data regarding a sequence of events, and it can assess causality. Furthermore, it is useful for investigating rare exposures and calculating rates of disease in exposed and unexposed individuals over time (Song & Chung, 2010). Importantly, Levin (2003) mentions that these studies can be expensive to carry out and are prone to high dropout rates (Levin, 2003). This wasa limitation in this current study as dropout rates were high, as well as it was expensive to conduct. Levin (2003) further mentions that prospective designs are mostly longitudinal but may be cross-sectional.

5.2.5. Cross-Sectional

One of the most common and well-known study designs is the cross-sectional study design. In this type of research study, either the entire population or a subset thereof is selected, and from these individuals, data are collected to help answer research questions of interest. It is called cross-sectional because the information about X and Y that is gathered represents what is going on at only one point in time (Olsen & St. George, n.d). A cross-sectional study often has predictive limitations and is often more expensive. Furthermore, the disease process may alter the exposure, affecting the overall resulting, and there is little or no data on the temporal relationship between risk factors and disease development (Ford, 2010).

This study was cross-sectional as it was carried out over a three-month period (out of the entire 18-month to two-year treatment period) for each participant (unless dropout or withdrawal from the study). The pharmacokinetic measurements and audiological data were collected at specific points in time.

5.2.6. Case Series

A case series design was employed, which is a design that follows a group of patients who have a similar diagnosis or who are undergoing the same procedure over a specified period. As there is no experimental protocol or control for allocation of patients to treatment, medical professionals decide on whether treatment is given, making the clinical sample representative of a typical clinical population. Results of case series, as with this study, can generate hypotheses that are useful in designing further studies, including randomised controlled trials. However, no causal inferences should be made from case series regarding the efficacy of the investigated treatment (Kooistra, Dijkman, Einhorn & Bhandari, 2009).

5.3. Research Sites

Data collection took place at two of three main hospital-based TB focal points that treat DR-TB patients in the Johannesburg area of the Gauteng Province in South Africa, namely the Helen Joseph Hospital TB Focal Point and the South Rand Hospital TB Focal Point. Post ethical clearance (Appendix A), permission was obtained from the CEOs (Appendix B).

The first site was the TB focal point at the Themba Lethu Clinic at HJH. Helen Joseph Hospital provides services to approximately 1 million people. HJH consists of a total of 21 wards with in-patients, the majority of which are medical wards, a Psychiatric unit, a 10-bed Intensive Care Unit (ICU), a 12 bed-High Care/ Step-down unit, a Theatre complex comprising of 12 theatres. HJH also includes speciality clinics including Stoma unit, Renal dialysis unit, Pain clinic, Endoscopy unit, Breast clinic, the TB focal point and the Themba Lethu HIV clinic (Gauteng Department of Health, n.d.)

The Themba Lethu Clinic is one of the country's oldest HIV treatment clinics. The clinic was established in 1992, in response to the threat posed by HIV in the days when ART was not available in South African public healthcare facilities. The clinic operates as a partnership between HJH and Right to Care, a non-governmental organisation whilst academic, clinic, and research support is provided by the Clinical HIV Research Unit (CHRU), which is affiliated to the University of the Witwatersrand. The Themba Lethu Clinic offers integrated services to patients with HIV and TB. In addition to HIV counselling-and testing, TB screening, diagnosis, and treatment is provided that includes a decentralised DR-TB management program. The clinic annually performs over 10 000 HIV tests, 4000 TB screens, and 4000 CD4 counts (Clinical HIV Research Unit, 2012).

AT HJH, patients enrolled for RR-TB management are provided with a scheduled appointment date to return to the clinic two weeks after RR-TB treatment initiation and then

every four weeks for 18 - 24 months. The patients can also choose whether they want to attend the HJH RR-TB clinic or an alternative primary healthcare clinic closer to their home for daily directly observed treatment support and injections during the intensive phase (Gajee et al., 2016).

The second site was the South Rand Hospital, a level one district hospital that opened in 1954. This hospital is situated on the outskirts of Johannesburg South. The hospital has 314 beds and serves a population of ± 450 000. In addition to being one of five rehabilitation hospitals in Gauteng, it is also one of two Gauteng-based hospitals that treat DR-TB patients on both an out- and in-patient basis. It is in partnership with the University of the Witwatersrand to provide a TB centre of excellence, along with other centres of excellence, such as a virology and mother and child centres of excellence (Gauteng Department of Health, n.d.) The treatment period for DR-TB at this hospital ranges from between two and eight weeks. The hospital has two DR-TB wards, one male and one female ward and serves as a referral site from many outlying hospitals.

5.4. Participant selection and description

5.4.1. Participant selection

5.4.1.1. Sampling strategy.

Sampling involves the selection of a portion of a limited population being studied (Battaglia, 2008). This study utilised a purposive sampling, a non-probability sampling strategy to select participants.

Non-probability sampling is a type of participant sampling does not involve random selection from the population. Thus, certain members of the population have a greater chance of selection for a study than others. It is often used to gain insight into a variety of specified issues (Skowronek & Duerr, 2009). This method of sampling is, however, susceptible to bias

because it does not guarantee that all eligible members of a population have an equal chance of selection into the sample (Skowronek & Duerr, 2009).

This study utilised purposive sampling, a type of non-probability sampling (Teddlie & Yu, 2007). The primary objective of purposive sampling is to produce a sample considered as ‘‘representative’’ of the population (Battaglia, 2008). It is used to address specific purposes related to research questions (Teddlie & Yu., 2007). The selection of a purposive sample is often accomplished by applying expert knowledge of the population to select in a -non-random manner a sample of elements that represent a cross-section of the population. Purposive sampling took place as the researcher selected the population of interest based on various factors, such as a predisposition to hearing loss (such as due to previous aminoglycoside use) and other inclusion and exclusion factors such as diabetes, middle ear dysfunction and so on that could influence the study outcomes (Battaglia, 2008).

A clear limitation of purposive sampling is that another expert (audiologist) may come up with a different sample when identifying important characteristics and select common elements to be in the sample. However, in the instance of this study, various audiologists and professionals working within this population were consulted (Battaglia, 2008).

Another limitation is that it does not necessarily allow for generalisation (Brink, 1996). This study was conducted in Johannesburg, Gauteng and the results cannot necessarily be generalised to other regions within South Africa.

5.4.1.2. Inclusion and exclusion criteria.

Participants had to meet specific selection criteria for inclusion in the study (See Table 5.1 for inclusion criteria and Table 5.2 for exclusion criteria). Previously, the study coordinator obtained consent to assess whether they fit the criteria (Appendix C). The study coordinator determined these inclusion criteria, who was a professional nurse. She

determined whether the participants met the inclusion and exclusion criteria. The criteria, justifications, and method for choosing and ensuring the inclusion and exclusion criteria can be seen below.

Table 5.1

Inclusion Criteria of participants in the sample

Criteria	Justification	Method
Both male and female participants	Male and females have shown to display slight differences in hearing, specifically in the high frequencies where the male population displays poorer hearing (4 kHz to 8 kHz) (Osterhammel & Osterhammel, 1978). Gender differences have also been shown to affect otoacoustic emission (OAE) results, with regards to phase delay (Bowman, Brown & Kimberley, 2000).	Both genders were considered for the study. At SRH, recruitment took place from both the male and female wards.
Both HIV-positive and HIV-negative patients.	HIV can cause opportunistic infections and neural disturbances that may place participants at greater risks for hearing loss (Friedmann & Arnold, 1993). However, excluding participants based on HIV status would have reduced the sample size, due to the high HIV prevalence within the DR-TB population.	The patient's HIV status was detailed in the consent procedure where participants were informed about the criteria, and the necessity of the researcher to know their HIV status; whether they were positive or negative. As per the NDoH (2011) guidelines, all HIV infected patients who are not on ARV therapy should be initiated on this treatment once drug-resistant TB is diagnosed. This was done accordingly.
Consent to HIV test (if one not already present)	If participants did not have a documented HIV test, they were requested to consent to an HIV test. This was a requirement of the study and thus conducted in the screening procedures. If	When their HIV status was not available, and consent was given, HIV testing, counselling and initiation of treatment was done according to NDoH protocols.

Criteria	Justification	Method
	they did not wish to consent, they were not included in the study.	
Written informed consent	Consent forms part of ethical practice for clinical research (SA GCP, 2006).	This was done according to the South African Good Clinical Practice guidelines (SA GCP, 2006).
Patients treated at HJH and SRH and anticipated to return for treatment for three months.	As HJH and SRH are two of the main sites of DR-TB treatment in Johannesburg, they were chosen.	The study coordinator was in constant communication with the nursing staff involved in new intake of all new intake patients at these hospitals to ensure enrolment when possible
Patients who were anticipated to be receiving treatment for DR-TB with KM and/or CM for a period of at least three3 months.	As the study was investigating the injectables, those patients on kanamycin or capreomycin were included.	The treatment plan and specific injectable were discussed by the study coordinator with the doctor prior to enrolment, to ensure that the participant was to be treated with either kanamycin or capreomycin.
Proficient in English, isiZulu or SeSotho	For informed consent to be carried out appropriately, the participants' comprehension must be addressed. In South Africa, this must be conducted by using culturally accepted	The study coordinator obtained details regarding the participant's language of choice during the screening procedure.

Criteria	Justification	Method
	practices and the participant's language of choice (SA GCP, 2006). According to the South Africa Statistics in the 2011 Census in the provincial profile, English (20.1%), isiZulu (23.4%) and SeSotho (9.6%) were the top three spoken languages in Johannesburg (Stats SA, 2011). Thus, proficiency in the top three languages was required for the study coordinator to be fluent.	She asked which language was the patient comfortable in and would prefer the discussion about the research to be in.
Between the ages of 18 to 55 years	Presbycusis usually presents in the fifth decade of life, generally above 55 years of age (Arvin, Prepageran & Raman, 2011). As all participants were required to give informed consent to participate in the study, the minimum age of 18 years was selected as all adults are assumed to have the capacity to consent unless otherwise proven.	The participant's date of birth was obtained during the screening procedure. Identification documents were checked to confirm to date of birth.
Normal middle ear status at baseline as determined by otoscopy and tympanometry.	An abnormal Tympanogram can indicate middle ear dysfunction which could affect DPOAEs as well as PTA. This is because OAEs cannot be conducted reliably as the presence of middle ear pathology results in severely diminished OAEs (Swanepoel et al., 2007). Furthermore, a conductive hearing loss is often indicated by air conduction threshold that is worse than the bone conduction	Hearing screening was conducted once consent was obtained. Screening measures included otoscopy, tympanometry, and PTA. Normal middle ear status for this study was classified as: • Type A tympanogram [ECV of 0.2 to 2.0 ml, SC of 0.2 to 1.8 ml; MEP of +50 to -100daPa (Jerger, 1975)],

Criteria	Justification	Method
	threshold. Conductive losses are associated with outer and middle ear systems (Moore & Zouridakis, 2003).	• Type As with a slightly decreased static compliance, however, not yet flat compliance as with a Type B tympanogram (Martin & Clark, 2003) or a • Type Ad with slightly increased static compliance. Patients with Type B tympanograms (flat compliance) or Type C tympanograms (negative pressure) were excluded but were referred for medical management. Participants who developed middle ear infection during the course of their treatment (and research) were not excluded.
Patients with no hearing loss of >70 dB at 3 or more frequencies bilaterally	Ototoxic hearing loss can vary in the degree of the loss. The audiometer can only record hearing loss up to 110 dBHL. Should a severe hearing loss (70 dB) worsen by more than 40 dB, it cannot be recorded. Any hearing loss with a lesser degree of severity at baseline would have a broader range to allow accurate measures.	Screening audiometry was conducted by the study coordinator to ensure the hearing was within these limits.

Table 5.2

Exclusion Criteria of participants in the sample

Criteria	Justification	Method
Diagnosis of Diabetes Mellitus	Diabetes Mellitus has shown to cause hearing impairment, and this would have impacted on the reliability of the results (Kakarlapudi et al., 2003).	Potential participants were asked if they had diabetes during the screening procedure. If they had diabetes, they were then excluded.
Limited language Proficiency in English, isiZulu and/or SeSotho	In order for informed consent to be carried out appropriately, the participants' comprehension must be addressed. In South Africa, this must be conducted by using culturally accepted practices and the participant's language of choice (SA GCP, 2006). According to the South Africa Statistics in the 2011 Census in the Provincial Profile, English (20,1%), isiZulu (23.4%) and SeSotho (9.6%) were the top three spoken languages in Johannesburg (Stats SA, 2011). Thus, proficiency in the top three languages was required for the study coordinator to be fluent.	The study coordinator obtained details regarding the participant's language of choice during the screening procedure. She asked the language of preference and subsequently conducted the informed consent procedures in this language. Should the language of preference not be either English, isiZulu or SeSotho, the potential participant was not included in the study.
History of significant substance abuse (alcohol and/or drugs)	Substance abuse is associated with poor medication adherence (Magura, Rosenblum & Fong, 2011). If the participant was not adherent to the DR-TB treatment regimen, it could have affected the outcomes of the study.	The study coordinator gauged this during the screening procedure. She enquired regarding alcohol use, frequency, and type as well as substance abuse in the case history. The study coordinator had been involved in several drug trials previously and also used her experience to gauge this.

Criteria	Justification	Method
Intravenous treatment with aminoglycosides and/or polypeptide within the last seven months. These drugs included capreomycin, kanamycin, amikacin, gentamicin, tobramycin, neomycin or streptomycin	Aminoglycosides can stay in an individual's system for six months and possibly cause ototoxicity (Mudd et al. 2016). As the focus of the study was capreomycin and kanamycin, possible effects of previous aminoglycoside toxicity needed to be excluded.	The study coordinator obtained a comprehensive medical history from potential participants which included previous treatment (See Screening Case Report forms in Appendix D). This was confirmed by reviewing the participants' available medical records. Individuals who were treated with intravenous aminoglycosides and/or polypeptide within the last seven months were excluded from participation in the study.
Patients with hearing loss of >70 dB at three or more frequencies bilaterally	Ototoxic hearing loss can vary in the degree of the loss. The audiometer can only record hearing loss up to 110 dBHL. Should a severe hearing loss (70 dB) worsen by more than 40 dB, it cannot be recorded. This would thus have impacted the validity of the measures, as should the hearing loss progress even more than 40 dB; it could not have been documented with these audiometric measures.	The study coordinator conducted screening audiometry to ensure the hearing was not greater than 70 dB at three or more frequencies bilaterally.

5.4.2. Sample Size

The initially proposed sample size was 80 participants from HJH. Based on the number of patients admitted to HJH, the number of patients that may have been eligible to participate, in combination with the various extraneous variables, attrition, and incidence of reported hearing loss, the sample size was estimated to be 80 participants when accounting for dropout (See Table 5.3). Therefore, 80 participants were intended for enrolment. From the time of enrolment, each participant was to be followed for three months or until death or withdrawal from the study. Based on expected dropout, about 60 participants were expected to complete the three-month period based on the table. Drop out from all causes was estimated at 30%.

This total sample size of 60 was calculated using a power calculation. This calculation included the above criteria of a significant change of hearing as described by Konrad-Martin et al., (2005) according to the ASHA (2004) guidelines, with a standard deviation of 1-5dB SPL and ≤10dB HL for DPOAEs and pure tone audiometric measurements respectively.

With a sample size of 60 patients a two-sided two-tailed t test at the 5% level of significance would have 99% power to detect a mean difference of 10db with the pure tones assuming a common standard deviation of 10dB. The same test would have 90% power to detect a mean difference of 6dB with the DPOAEs assuming a common standard deviation of 10dB.

Table 5.3

Original expected reasons for withdrawal from the study

Reason withdrawal from study	Frequency (%)
Loss to follow-up	10
Transfer out	10
Other	10
All causes (total)	30%

After six months of recruitment at HJH, a decision was made to also include SRH as a second site as the proposed sample size could not be achieved at only one site. Permission was obtained to recruit participants at South Rand Hospital.

South Rand Hospital treats patients on an inpatient regimen for two to eight weeks. SRH initially appeared as an ideal recruitment site. However, SRH often treated with capreomycin; injectable that is not as ototoxic as kanamycin.

Although this inpatient regimen was more ideal for participant treatment, it did create more variability in the study. However, this variation was unavoidable, especially as capreomycin, although more expensive, and thus rarely used at other hospitals, is a less toxic drug for patients.

Permission was obtained from the hospital, however, a few protocols needed to be adjusted to fit within this hospital structure. This included the use of capreomycin, as well as the need to conduct more study related creatinine blood tests, as they were not done as frequently at SRH as at HJH as part of the standard of care. Ethical clearance was also reobtained to include this new study site and adjusted protocol.

Nevertheless, despite the hospital treating patients with an inpatient regimen, recruitment and enrolment were not as successful as hoped. After 12 months of recruitment at HJH (January to December 2015) and six months at SRH (July to December 2015), enrolment was only at 22 participants. Only a few of these participants completed the full 12-week period of data collection.

The reasons for not achieving the sample size are outlined in Table 5.4.

Table 5.4

Detailed Potential Participant Enrolment Description

	HJH[1] ***n***	**SRH[2]** ***n***
No. of DR-TB patients initiated on treatment at research site	137	131
No. of potential participants approached	36	46
No. of participants enrolled	9	13
No. of participants dropped out before 12 weeks	4	12
No. of participants who completed the study	5	1
Reasons for exclusion before approaching potential participant		
• Not within study age range	5	8
• Diabetic	0	1
• Pregnant	1	1
• Previous defaulters on regimen two	6	26
• Live too far to return for follow-up visits	48	
• History of substance abuse	1	13
• Participating in other studies	35	
• Renal Problems	5	7
• Transferred out		29
Total excluded prior to approaching patient	101	85
Participants approached to participate in the study	36	46
Reasons for exclusion once potential participant was approached		
• Too ill to undergo consent process and initial baseline testing	7	13
• Presence of middle ear pathology at the time of enrolment	2	2
• Keen to participate however did not return the following day for baseline measures (reason unknown)	8	
• Refused to participate	10	18
Total excluded once approached	27	33
Total Remaining Participants	9	13

Note: [1] January to December 2015, [2] July to December 2015

Twelve months after the initiation of recruitment, enrolment ceased due to limited resources and the view that statistically, saturation was adequate for a feasibility study. Funding for the salary of the study coordinator was limited due to an initial 12 months' contract and the audiological equipment made available by Amtronix for a period of 18 months had to be returned to the company. The study coordinator was funded for a year to assist with procedures. After this time, she started assisted with another study. The researcher could not fulfil her role as she is not a trained phlebotomist and not fluent in all the languages needed to conduct informed consent. Although the researcher would have liked to continue enrolment, it was suspected that by enrolling for another six to 12 months would not yield considerable more data (due to the other studies).

The final sample size comprised 22 participants followed for three months or until dropout. A total of 80 study visits were completed. Only a few of these participants completed the full twelve-week period of data collection.

Although this study had a small sample size, it is essential to place the sample size in the broader context of TB treatment adherence, where adherence is often poor (Gajee et al., 2016). A systematic review demonstrated poor adherence, from which three central themes stemmed; health services factors, social factors (family and community structures) as well as the financial strain of the treatment process (Munro, Lewin, Smith & Volmink, 2007). Furthermore, Gajee et al. (2016) found that 53.5% of patients missed one or more appointments during outpatient treatment at HJH, which is of concern.

5.4.3. Participant Description

The mean age of participants at baseline was 33.78 years (Range: 18.6 – 42.8y; ± 7.3). The mean age of the participants at HJH was 29.56 years (Range: 18.6 - 40.7; ± 7.59). The mean age of the participants at SRH was 36.71 years (Range: 22.4 - 42.8; ±5.73).

The general description of participants including gender, treatment status, marital status, the language of choice, and employment status (at baseline) are detailed in Table 5.5.

Table 5.5

General Description of the Participants (n = 22)

General Description		HJH	SRH	Total
Gender	Male	3	4	7
	Female	6	9	15
Treatment status	Inpatient	0	13	13
	Outpatient	9	0	9
Marital status	Married	2	1	3
	Single	6	10	16
	Cohabitating	1	2	3
Language of choice	English	3	5	8
	SeSotho	0	1	1
	isiZulu	0	2	2
	English & SeSotho	2	1	3
	English & isiZulu	4	1	5
	English, SeSotho & isiZulu	0	3	3
Education	Grade 10	6	4	10
	Grade 11	2	4	6
	Grade 12	1	3	4
	Tertiary	0	2	2
Employment Status	Employed	2	4	6
	Unemployed	7	9	16

Furthermore, the participant's audiological history can be seen in Table 5.6. The most prominent aspect was that 8 participants reported struggling with localising sound at baseline.

Table 5.6

Audiological History of the patients in this study

Audiological History	HJH *n*	SRH *n*	Total *n*
Previous Ototoxic Medication	0	2	2
Previous Hearing Test	1	0	1
Struggle to Hear at Baseline	0	1	1
Family History of Hearing Loss	1	2	3
History of Noise Exposure	2	1	3
Tinnitus	0	1	1
Difficulty Localizing	4	4	8

Majority of participants were HIV positive (81%), as expected. However, the majority (50%) were not on ARVs at baseline. Subsequently, their treating doctor initiated ARV treatment. This is evident in Table 5.7.

Table 5.7

The number of patients' HIV Infection and Treatment Regimen.

HIV infection and Treatment Regimen at baseline	HJH *n*	SRH *n*	Total *n*
Positive	7	11	18
Negative	2	2	4
On treatment	3	6	9
No treatment (if positive)	4	5	9
EFC, TDF, 3TC	0	4	4
FDC	0	1	1
FDC, FTC, TDF	0	1	1
Nevirapine, TDF	1	0	1
TDF, ATV, RTV	1	0	1
EFC, d4T, 3TC	1	0	1

Note: Abbreviations in Table 5.7: EFV: efavirenz, TDF: tenofovir disoproxil fumarate, 3TC: lamivudine, D4T: stavudine, FDC: emtricitabine, ATV: atazanavir, RTV: ritonavir

Medical history of participants is described in Table 5.8. In conjunction with table 5.8, no one had a history of cancer, measles, mumps, significant ear infections, encephalitis, meningitis, diabetes, endocrine, cardiovascular (CVS), central nervous system (CNS) or gastrointestinal (GUT) problems. Furthermore, no participants reported any other medication at baseline, apart from ARVs, as described above.

Table 5.8

Detailed Medical History of Participants

History	Description	HJH	SRH	Total
		n	*n*	*n*
Smoking	History of Smoking	6	9	6
	Presently Smoking	0	1	0
Alcohol	Drink at Present	4	7	4
Previous Surgery	Gallstones, Laparotomy, Gunshot, C-Section, Unknown	3	8	3
Previous Head Injury	Types Unknown	2	2	2
Allergies	Tinned Fish	0	1	0
History of GUT Problems	None	7	7	7
Dermatological Problems at Baseline	Circular Hyper-Pigmented Lesion, Hyper Pigmented Rash: face, hand, trunk	0	2	0
Other Observations at Baseline	Bilateral parotid lymphnode	0	1	0
Weight (kg)	Mean	51.66	57,13	54.83
	Range	42-59	34-73	34-73
	SD	5.10	14.07	11.31

5.5. Data Collection

Data collection included a variety of procedures and involved a team of personnel. Firstly, an overview of the data collection process is described, followed by a description of

the research team involved in this process. Then, the data collection procedures are described, including the audiological, pharmacological and medical aspects.

5.5.1. Data Collection Overview

Data collection consisted of a number of procedures that needed conducting at specific time intervals with each participant. Therefore, a schedule of the procedures and time intervals was drawn up and followed for each participant. The standard of care procedures includes the procedures that take place at the hospital as part of their general standard of care. This included the measurement of weight, height, HIV status, creatinine, CD_4 count, Potassium, Thyroid Stimulating Hormone (TSH), Liver Enzymes and a full blood count. Thus, at times, procedures were not conducted as part of the study protocol as the results were utilised from the standard of care procedures. Creatinine was not always conducted as part of the study because at times, it was conducted as part of the standard of care at the hospital. The protocol differed slightly between HJH and SRH due to their slight variation on the standard of care procedures (Table 5.9).

Table 5.9 provides an overview of the protocol data collection procedures. Details in the table are included for the 2-week intervals. Although not included in the table, there were daily and weekly procedures to be carried out.

The daily procedures included the administration of kanamycin/capreomycin at either SRH, HJH, or at the local clinics, and documented in the drug diary. Furthermore, the study coordinator or local clinic nurse at the various outpatient clinics were required to complete a drug ‘diary’ daily, specifying the time and dosage of kanamycin/capreomycin, and the concomitant medications.

The weekly or twice weekly procedures involved sending the blood samples to SMU in bulk from all the participants, depending on the availability of the driver.

Lastly, money was provided to participants as will be in the data collection procedure below.

It was only provided for the outpatients.

Table 5.9

Data Collection Overview

Evaluations	**Screening and Baselines**			**Follow Up Visits**					**Final Visit**
	Day 1 (T0)	**Day2 (T0)**	**Day 3 (T0)**	**Day 15 (T1)**	**Day 28 (T2)**	**Day 40 (T3)**	**Day 54 (T4)**	**Day 68 (T5)**	**Day 84 (T6)**
	Screening	**Baseline**		**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Window		0 days (if clinic pt.) ±3 days (if ward pt.)	(must be the day after day 2)	±3 days					
Standard of Care	✓								
Weight	✓			✓	✓		✓		
Height	✓								
HIV status	✓								
Creatinine (Cr, GFR) (Helen Joseph)	✓			✓			✓		
Creatinine (Cr, GFR) (South Rand)	✓								
CD4	✓						✓		
Potassium (K)	✓						✓		
TSH	✓								
Liver Enzymes (GGT, ALT, Bili)	✓								
FBC	✓								

Evaluations	Screening and Baselines			Follow Up Visits					Final Visit
	Day 1 (T0)	**Day2 (T0)**	**Day 3 (T0)**	**Day 15 (T1)**	**Day 28 (T2)**	**Day 40 (T3)**	**Day 54 (T4)**	**Day 68 (T5)**	**Day 84 (T6)**
	Screening	**Baseline**		**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Case Report Forms									
Screening/Eligibility Consent	✓								
Informed Consent	✓								
Medical History	✓								
Medication History	✓								
Baseline Case Report Forms	✓								
Follow up Case Report Forms				✓	✓	✓	✓	✓	✓
Pharmacological									
Peak		✓		✓	✓	✓	✓	✓	✓
Trough			✓	✓	✓	✓	✓	✓	✓
Creatinine (HJH)*					✓	✓		✓	✓
Creatinine (SRH)*				✓	✓	✓	✓	✓	✓
HIV Confirmation (if necessary)			✓						
Package & Refrigerate		✓	✓	✓	✓	✓	✓	✓	✓
Audiology									
Screening Audiology (Otoscopy, tymp, pure tones, Cerumen Mx if needed)	✓								

Evaluations	Screening and Baselines			Follow Up Visits					Final Visit
	Day 1 (T0)	Day2 (T0)	Day 3 (T0)	Day 15 (T1)	Day 28 (T2)	Day 40 (T3)	Day 54 (T4)	Day 68 (T5)	Day 84 (T6)
	Screening	Baseline		Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Cerumen Mx (if indicated)	✓	✓		✓	✓	✓	✓	✓	✓
Case Report		✓		✓	✓	✓	✓	✓	✓
Otoscopy		✓		✓	✓	✓	✓	✓	✓
Tympanometry		✓		✓	✓	✓	✓	✓	✓
DPOAEs		✓		✓	✓	✓	✓	✓	✓
PTA		✓		✓	✓	✓	✓	✓	✓
Other									
Administer Kanamycin/Capreomycin		✓	✓	✓	✓	✓	✓	✓	✓
Weight		✓	✓			✓		✓	✓
Money to participant (if outpatient) #	✓	✓	✓	✓	✓	✓	✓	✓	✓
Appointment Card for Next Visit	✓	✓	✓	✓	✓	✓	✓	✓	✓

Note: *The protocol differed slightly between HJH and SRH due to their slight variation on the standard of care procedures. South Rand Hospital conducted creatinine measurements as part of the standard of care at baseline, where Helen Joseph conducted creatinine measures more frequently as part of the standard of care. Therefore, the study protocol included more creatinine tests at South Rand to compensate for the lack of measures as part of the standard of care.

#Although weight was measured as part of the standard of care; this was not at every study visit. Hence the measurement of weight and height were included in study related procedures.

5.5.2. Research team

This study was a multidisciplinary study, including pharmacology, audiology, and medicine. Therefore, the research team consisted of experts in these fields, as well as significant support and administrative staff. All the roles were defined clearly prior to the study to ensure valid and reliable results. The research team consisted of:

- **Principal Investigator**: A medical doctor whose extensive experience as an investigator in clinical drug trials at Wits Health Consortium CHRU was appointed to oversee the study. The principal investigator was responsible for all the participants' DR-TB treatment at HJH. As the principal investigator did not have authority at SRH, the treating doctors at SRH were thus responsible for the SRH participants.
- **Medical Doctors/Specialist Physician**: Two medical doctors (SRH) and one specialist physician (HJH) were responsible for the daily and overall management of the participants.
- **Biochemist and Laboratory Personnel***:* The biochemist and laboratory personnel from the Sefako Makgatho Health Sciences University (SMU) assisted in the development of the procedure for the measurement of kanamycin pharmacokinetics in patients with DR-TB specifically for this study.
- **Clinical Pharmacist/s**: The clinical pharmacist and specialist in pharmacokinetics from the SMU conducted the pharmacokinetic calculations of the kanamycin and capreomycin and interpreted the results.
- **Audiologist and researcher**: The audiologist/researcher was responsible for the development of the protocol and standard operating procedures, obtaining relevant permissions and ethical clearances. This also included the training of relevant personnel according to the study protocol and standard operating procedures, quality

assurance (QA), continuous monitoring and management of the study and issues, coordination and funding for the study.

- **Statisticians and Epidemiologist**: An independent bio-biostatistician/epidemiologist from Right to Care NGO was involved with the statistical plan in the development of the protocol and well as was involved with the final statistical analysis of the study. An independent, experienced statistician at the University of The Witwatersrand was also involved with the protocol development and final analysis and interpretation of the results.
- **Study Coordinator**: The study coordinator was a nurse from Right to Care TB Focal Point and was employed on a full-time basis (5 days per week) for the duration of the study's training and data collection (15 months). The study coordinator is an experienced research nurse in this field, with eight years' experience in research at the start of the study. She received comprehensive training (with complete training manual - available on request) on how to perform the audiological measures and how to communicate with individuals with a hearing loss. The study coordinator was responsible for participant recruitment and enrolment, the informed consent process, drawing and packaging of blood, audiological measures, other measures such as weight and height, collating the information from the patient files, case history and follow-up records, various administrative duties, communication between the pharmacist and doctors and follow-up procedures. The study coordinator moved between HJH and SRH for five days a week full time to conduct the study-related procedures and ensured all procedures were done according to Good Clinical Practice (GCP) guidelines (SA GCP, 2006).
- **Local Clinic Nurses**: A specific nurse was assigned from the local clinic to inject the participants daily with their dose of kanamycin or capreomycin and documented the

time and dosage in the drug diary. These clinics were identified as the clinic closest to the patient's residence, where they received their daily, outpatient injections.

- **Hospital-Based Nurses**: The nurses in the wards were required to notify the study coordinator as soon as a patient with DR-TB was admitted, and prior to the initiation of kanamycin or capreomycin, if possible. The nurses at HJH and SRH were required to treat the patients as per hospital protocol and communicate relevant information to the study coordinator collecting data for this study.
- **Quality Assurance (QA): Personnel**: The QA team at CHRU checked that the informed consents were complete and done according to GCP guidelines at HJH. The study coordinator and researcher performed QA procedures at SRH when the CHRU team was not available.
- **Phlebotomists***:* The phlebotomists at CHRU assisted with the drawing of blood when necessary and centrifuged and stored the blood samples daily.
- **Receptionist***:* The receptionist at HJH provided payment for the outpatient participants.

5.5.3. Data collection procedures

The data collection procedures comprised participant recruitment, participant enrolment, and application of the research protocol which included audiological measures and pharmacological procedures. The recruitment and enrolment procedures obtained data and thus is considered part of the data collection procedures.

5.5.3.1. Participant recruitment.

Participant recruitment involved the study coordinator advertising the participation in the study at the various hospitals. Recruitment took place in the waiting room at HJH, and the wards at SRH. The study coordinator informed patients that a study about hearing was taking place, and participants were invited to participate in the study if they fulfilled specific criteria.

A brief and general description and overview regarding the study was provided, to establish whether patients were interested in possible screening and further enrolment.

5.5.3.2. Enrolment: screening for eligibility and consent.

After recruitment to the study, the screening process was conducted to ensure eligibility prior to the full consent forms and baseline measures. However, in order for screening measures to be conducted, a consent form for these measures needed to be administered. A screening consent form (Appendix C) was signed before the screening procedures (Appendix D). Only once the participant was eligible to participate, the full consent forms and baseline procedures were conducted (Appendices E and F). The details are below in Table 5.10

Table 5.10

Detailed Description of Screening and Baseline Forms of Eligibility

Screening measures of eligibility				
Category	**Appendix**	**Content**	**Rationale**	**Procedure**
Information Leaflet Screening Consent Form (English, isiZulu, and SeSotho)	C	Overview of the criteria for inclusion	These forms were used to obtain informed consent from potential research participants for the screening procedures in order to confirm eligibility. The consent process was conducted according to South African GCP standards (SA GCP, 2006) and adhered to the Declaration of Helsinki guidelines (WMA, 2013) for informed consent.	The study coordinator discussed the consent forms in detail with the participants and allowed for questions and concerns regarding the study in the potential participants' first language. If the potential participants' first language was not isiZulu, SeSotho or English, he/she was excluded, as a reliable informed consent could not be taken. Three forms were signed and placed in the 1) hospital file, 2) patients study file and 3) given to the participant.
Screening Case History/ Information and report forms	D	Name, Date of Birth, Race, Social History, Medical History, Surgical History, TB History, Pregnancy, Willingness to Consent to an HIV test, Language of proficiency, Checklist of previous possible ototoxic medications, Audiology History	The screening case history was conducted to confirm eligibility for inclusion.	The study coordinator asked potential participant all the questions and conducted the audiological screening measures. The answers and results were documented on the report form.

Baseline measures of enrolment				
Information Leaflet and Informed Consent Form (English, isiZulu, SeSotho)	E, F	This contained information regarding the purpose of the study, study procedures, risk add benefits, and all information regarding the process and procedures in the study.	These forms were used to obtain informed consent from research participants for the screening procedures in order to confirm eligibility. The consent process was conducted according to South African GCP standards (SA GCP, 2006) and adhered to the Declaration of Helsinki guidelines (WMA, 2013) for informed consent.	The study coordinator discussed the consent forms in detail with the participants and allowed for questions and concerns regarding the study in the potential participants' first language. If the potential participants' first language was not isiZulu, SeSotho or English, he/she was excluded, as a reliable informed consent could not be taken. Three forms were signed and placed in the 1) hospital file, 2) patients study file and 3) given to the participant.
Baseline Case Report Forms	G	The baseline case report forms detailed the procedure for the blood sampling (pharmacokinetics, HIV testing, and creatinine testing), audiology measures, as well as all the case histories and physical examinations	These forms were developed to record all baseline results to allow for comparison from the follow-up results.	The study coordinator conducted the procedures and completed the forms. The completed forms were filed in the participants' study file.
Patient Contact Information Form	H	Language of participant, contact phone number, new contact number (if changed during the study)	The participant's basic contact details were documented in every study file. It was imperative to have recent contact details for all participants in the event of follow-up for missed appointments.	The study coordinator recorded the participant contact details.

HIV Testing Consent Form	As per NDoH form	This form details the counselling discussion which includes the description of HIV and AIDS, risk factors, cure, the test procedures and interpretation of the results as well as the consent form.	When HIV data was not readily available, HIV testing was conducted for documentation as part of the study protocol.	Informed consent was done separately to this according to Department of Health Guidelines for HIV testing. However, Clinical Laboratory Services performed the analysis of the sample.

5.5.3.3. Detailed history.

Prior to the audiological and pharmacological data collection procedures, detailed case history questionnaires were administered. This occurred at the baseline measure. Subsequently, further case report forms were administered at the follow-ups to determine any changes. Details can are visible in Table 5.11

Table 5.11

Case History and Case Report Forms

BASELINE				
CASE HISTORY (appendix G)				
Category	**No. of Questions**	**Content**	**Rationale**	**Procedure**
Medical History	30	Head, Ears, Eyes, Nose, Throat, Neck, Cardiovascular System, Respiratory System, Gastrointestinal Tract, Urogenital Tract, Haematological System, Rheumatological System, Endocrine System, Central Nervous System, Dermatological System, Reticulo-Endothelial System, Allergies, Other problems, CD_4 count	The medical history of patients could impact their risk of hearing loss. In particular, patients were asked about their history of TB, measles, mumps, frequent ear infections, encephalitis, meningitis, cancer, trauma (especially to the head), and hospitalisations (Wood, 1979; Robinette & Cevette, 2002).	The study coordinator conducted a detailed interview with the participants and also reviewed participants' medical file (with participant permission). Both the medical history and audiological history were recorded on the specific history forms and placed within the participants' study file.
Auditory History	14	Previous medication, Family History of Hearing Loss, Otalgia, Otorrhea, Tinnitus, Dizziness, Aural Fullness, Hearing Loss, Noise Exposure	Audiological History can assist in identifying contributing factors of hearing loss (Robinette & Cevette, 2002).	

FOLLOW UP WEEKS (T1 to T6)			
CASE REPORT FORMS (Appendices H to M)			
Category	**Content**	**Rationale**	**Procedure**
Follow up Case Report Forms	Checklist of procedures, Inpatient/outpatient details, Interim medical history, Details of the last injectable, audiological, behavioural, psychological changes, willingness to continue participation, audiological measures record forms	The follow-up case report forms contained checklists to ensure all the measures were conducted and allowed accurate recording.	The baseline and follow up case report forms detailed the procedure for the audiology measures. The study coordinator completed them when doing the procedures. On day 84, the participant was referred to the audiology department within their district for further monitoring and hearing aid management. If the participant terminated the study earlier, they were referred earlier to an audiology department**.**

5.5.3.4. Audiological procedures.

Audiological testing was to be carried out every second week (Baseline and weeks 2, 4, 6, 8, 10 and 12). The total duration was three months or until dropout.

The audiological measures consisted of otoscopy, tympanometry, cerumen management (if indicated), PTA and DPOAEs. Testing was conducted in the same order for all the participants, with the left ear being tested first. Noise levels were monitored throughout, and universal infection control was carried out. The details can be seen in Table 5.12

Table 5.12

Audiological Measures and Equipment

Audiological Measures and Equipment			
Measure	**Equipment**	**Rationale**	**Description**
Otoscopy	Welch Allyn Pocket Otoscope Specula e	An otoscopic examination is performed to evaluate the state of the outer ear, and tympanic membrane for abnormalities and/or infection (Rappaport & Provencal, 2002).	Otoscopy is used to determine the condition of the external auditory meatus and tympanic membrane, to ensure that there were no obstructions in the external canal or conditions that may have influenced additional testing procedures (Rappaport & Provencal, 2002. The normal otoscopic examination was considered as a visible tympanic membrane, no perforations, cone of light, with no obstructions in the canal (besides for cerumen).
Cerumen management (if indicated)	YX932S Cerumen Suction Machine (supplied by Trojan Medical)	Impacted cerumen can affect the reliability of tympanometry and OAEs (Wilson & Roeser, 1997). Therefore, the removal of cerumen allowed for a clear external auditory meatus to assist in ensuring further reliable audiometric measures.	Cerumen management for cerumen occlusion of more than 70% was performed via the suctioning procedure. No participants however required cerumen management.
Tympanometry	Tympanometer (Maico Easytymp – supplied by Amtronix)	Tympanometry evaluates middle ear status through the depiction of tympanic membrane motility as a function of variations in air pressure (Clark, Roeser & Mendrygal, 2007). This test serves as an irreplaceable evaluative tool	The appropriate size nub was chosen, and the test was conducted according to the equipment's' procedure manual to ensure accurate outcomes.

Audiological Measures and Equipment			
Measure	**Equipment**	**Rationale**	**Description**
		representing middle ear functioning (Clark et al., 2007). The presence of middle ear pathologies results in severely diminished OAEs, and more severe cases may also influence the results obtained with ABR testing (Swanepoel et al., 2007), thus affecting the reliability of the OAE measures and air conduction PTA measures.	Normal middle ear status for this study was classified as: • Type A tympanogram [ECV of 0.2 to 2.0 ml, SC of 0.2 to 1.8 ml; MEP of +50 to -100daPa (Jerger, 1975) • Type As with a slightly decreased static compliance, however, not yet flat compliance as with a Type B tympanogram (Martin & Clark, 2003) or a • Type Ad with slightly increased static compliance.
Distortion Product Otoacoustic Emissions (DPOAE)	Otoread: High frequency, up to 12 kHz. Supplied by Interacoustics	OAEs were measured to obtain objective measures regarding the integrity of the cochlea (Prieve & Fitzgerald, 2002). Therefore, contributing to the differential diagnosis linked to auditory functioning at this level of the auditory system. They provide obtainable results for a wider range of hearing impairment (Prieve & Fitzgerald, 2002) and offer greater frequency specificity (Prieve & Fitzgerald, 2002).	DPOAEs were measured by placing a probe tip (of the appropriate size) in the patients' ear canal, presenting the tone into the external ear canal and measuring the distortion response obtained from the cochlea. The frequencies included: 2 kHz, 4 kHz, 6 kHz, 8 kHz, 10 kHz, 12 kHz Repeated measures were conducted, and noise levels were monitored throughput to ensure valid responses. This is an objective test as the participant was not required to respond.

Audiological Measures and Equipment			
Measure	**Equipment**	**Rationale**	**Description**
		DPOAE testing, prior to and after the treatment with kanamycin/capreomycin allowed the researcher to determine changes in amplitude related to the treatment with these drugs.	Responses were from +20 to -20, where -20 was considered absent. Selected appropriate SNR was +6 dB (see chapters 6 and 7)
PTA	Path Sentiero supplied by Amtronix Acer Laptop	PTA assesses hearing sensitivity as a function of frequency (Bess & Humes, 2008). This provides insight into the integrity of the auditory system as well as information relating to the symmetry, laterality, degree, and configuration of a patients hearing thresholds (Harrell, 2002). PTA can include air (AC) and bone conduction. Yet, only AC testing was done, as pure tone bone conduction (BC) thresholds cannot be done over 4 kHz. Generally, ototoxicity would begin in the high frequencies, and BC audiometry cannot assist in monitoring this. Bone conduction audiometry is often used to rule out conductive components; however, in this case, tympanometry was used to assist with this. Although BC would have been ideal, the participants	Frequencies tests included: 0.25, 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11.2, 12.5, 14 and 16 kHz. Response Mode: Press Button A mobile diagnostic audiometer was used so that testing could take place at the participants' bedside if necessary. This was important, as in the beginning stages when participants were hospitalised and were too sickly to leave their beds, testing could be done at their bedsides. A laptop was used to transfer the results to an excel spreadsheet for accurate recording, and to be placed in the study file. Change in hearing loss from baseline was recorded, and the overall hearing thresholds and norms were used to monitor the ototoxicity.

Audiological Measures and Equipment			
Measure	**Equipment**	**Rationale**	**Description**
		were sick and fatigued quickly, and thus reliable BC results were unlikely to be achieved.	
Noise Monitoring	ST-109 Type 1 integrating sound level meter, data logging with software and USB cable supplied by A.W.R. Smith Process Instrumentation cc	Noise levels were monitored throughout the testing with a sound level meter.	The sound level meter was placed next to the participant when conducted DPOAEs and PTA. Noise levels did not exceed 55 dB SPL.
Infection Control	Gloves, alcohol swabs, disinfectant, masks.	Infection control is essential to prevent the transmission of infection (Franklin& Grady, 2001) and allows for ethical and safe research.	Universal precautions were taken to ensure infection control.

5.5.3.5. Pure Tone Audiometry.

The ASHA guidelines for ototoxicity monitoring emphasise the increased test sensitivity achieved using ultra-high-frequency monitoring to detect ototoxicity (Konrad-Martin et al., 2005). With regards to the PTA results, frequency ranges were broken down into low frequencies (0.25 kHz until and including 2 kHz). Seddon et al. (2012) described that frequencies above 2 kHz are considered high frequencies (HFA). Thus, the analysis was investigated further from 3 kHz until and including 8 kHz; 8 kHz is where the conventional audiogram subsides and where speech frequencies generally care Then, as high frequencies are where ototoxicity is reported to start, further ultra-high (UHFA) frequencies were analysed in the PTA; from 9 kHz until and including 16 kHz.

Ototoxic HL as only confirmed should the above criteria occur from (and including) 2 kHz and above, or should the HL start at the higher frequencies and progress to the lower frequencies according to the ASHA criteria unilaterally or bilaterally. Test-retest differences for ultra-high-frequency thresholds using modern equipment are generally reported being within ±10 dB for frequencies between 9 and 14 kHz (Konrad-Martin et al., 2005). Therefore, the standard deviation (SD) for PTA was up to and including 10 dB.

5.5.3.6. Distortion Product Otoacoustic Emissions.

This probe emitted the stimulus of two ‘primary tones’ that vary in frequency and the cochlea responded by producing sounds. The microphone then picked these miniature sounds/emissions on the probe, and thus was a measurement of cochlear functioning, and not hearing, as hearing extends beyond the cochlea to the temporal lobe (Martin & Clark, 2003).

A clinically significant change can be classified as 6 dB SPL or greater. Therefore, variability in detection threshold or standard deviation is from 0 to 5 dB SPL (Roede et al., 1993). Determining effective ototoxicity detection and monitoring strategies using objective measures such as DPOAEs is an active area of research. However, there currently are no

accepted protocols or criteria for ototoxic change using DPOAEs. Most reports in patients receiving ototoxic drugs which have utilised objective measures such as DPOAEs, in which sensitivity was defined as a clinically significant change in the value of the objective measure (Konrad-Martin et al., 2005). Therefore, for this study, a clinically significant change that can be attributed to ototoxicity has been defined 6 dB or more at or above 2 kHz at one or more frequency unilaterally or bilaterally.

Both PTA and DPOAE measures were utilised to complement each other. PTA is a psycho-physical measurement of hearing with the aim of getting complete knowledge of an individual's ability to interpret various kinds of acoustic stimuli (Huizing, 1951), whereas DPOAEs have higher sensitivity than PTA in the monitoring of cochlear function (Sakashita et al., 1998), but not interpretation. As DPOAEs do not require an individual to respond physically, this can occur when the participant is too weak to participate in PTA. PTA was measured by placing earphones on an individual while the nurse/audiologist presented different pure tones with various frequencies to each ear via the earphones. The nurse/ audiologist needed to establish the individuals hearing threshold levels, i.e. the softest sounds that the individual can respond. Whereas, with DPOAEs, the nurse/audiologist placed a probe in an individual's ear.

5.5.4. Pharmacological and Laboratory Measures and Equipment

The pharmacological tests included the HIV (when no results were available) and creatinine testing as well as the pharmacokinetics of kanamycin and capreomycin. Moreover, in order to analyse the blood, various types of equipment needed to be purchased. The pharmacological equipment that needed to be obtained can be seen in Table 5.13.

Table 5.13

Pharmacological Equipment

Item/s	Discussion of Item/s
Liquid Chromatography-Mass Spectrometer (LC-MS)	**Aim:** An LC-MS combines the chemical separating power of LC with the ability of an MS to detect and confirm molecular identity selectively. **Rationale:** Mass Spectrometry is one of the most sensitive and highly selective methods of molecular analysis and provides information on the molecular weight as well as the fragmentation pattern of the analyte molecule. The information obtained from MS is invaluable for confirming the identities of the analyte molecules. **Use:** The mass spectra of various components present in medicines have been obtained online from the LC-MS run and matched with known standards for structural confirmation. Integrated MS databases have also been used for identification of various compounds. In this way, GC-MS, LC-MS, and MS-MS fingerprinting profiles of the active ingredients of various medicines have been obtained, and information has been stored in the form of an electronic database, which can be used for routine comparison of chemical profiles of individual compounds for quality control purposes.
Fridge/ Freezer	This fridge was needed to store blood samples before they were sent to SMU for analysis (between 2 and 8^{o}C). The samples were stored in a fridge if they were kept for seven days or less and in a -80 ^{o}C freezer if they were stored for more than seven days. The samples sent to CLS were not stored and sent immediately for analysis.
Other (scale, consumables for blood tests and infection control) Acer Laptop	This included: alcohol swabs, disinfectant, needles, syringes, red top tubes, yellow top tubes, storage containers, scale, stickers for the tubes, packets, and plasters. A computer was necessary for the study for a variety of reasons: to access the creatinine and lab results for the participants from the National Health Laboratory Service, to download the audiological results from the path Sentiero, electronic communication between all the parties involved in the research and to organize a weekly schedule of events of all the participants.

In order for these tests to be executed reliably, correct documentation was needed to record the blood being drawn and results. Also, for reliable results, it was essential to know the dosages administered daily, hence drug diaries were implemented (Table 5.14).

Table 5.14

Description of Pharmacological Forms and Case Report Forms for weeks T1 to T6

Category	Appendix	Content	Rationale	Procedure
Follow up Case Report Forms	I to N	Checklist of procedures Inpatient/outpatient details Interim medical history Physical Examination Details of last injectable Behavioural, psychological changes Willingness to continue participation	The follow-up case report forms contained checklists to ensure all the measures were conducted and allowed accurate recording.	The baseline and follow up case report forms detailed the procedure for the blood sampling (pharmacokinetics, HIV testing, and creatinine testing) as well as all the case histories and physical examinations. The study coordinator completed the forms when doing the procedures.
Daily Drug Diaries	O, P	Daily Drug Diary for Hospital and Study File Daily Drug Diary for Clinics The daily drug diaries for hospitals and clinics documented the dosage and times the injectables were injected • This allowed the researcher to track missed dosages.	The kanamycin and capreomycin dosing details (times and dosage) were explicitly essential to understand the pharmacokinetic results.	Drug diaries were either completed daily at the hospital when the study coordinator administered the injectable or at the local clinic when the injectable was administered at the clinic. The hospital drug diary was more detailed as the study coordinator was completing it; however, less information was obtained due to the time constraints of the clinic nurses.

Laboratory Requisition Form for Creatinine and HIV Testing (CLS)	Q	The requisition forms included participant identification details, weight as well as details of the test to be done and of the sample taken.	This form allowed for the documentation the specific test requested and specific week for the HIV tests and/or creatinine to be sent with the blood samples to CLS.	The study coordinator completed the form when the blood was drawn and sent it with the sample/s to CLS.
Laboratory Requisition Form for Kanamycin and Capreomycin Pharmacokinetics (SMU)	R	The requisition forms included participant identification details, weight, details of the sample that was drawn (date and time of collection) as well as details of the test to be done.	These forms allowed for the documentation of the date and time that blood had been drawn for the pharmacokinetic measures to be sent to SMU with the relevant blood samples	The study coordinator completed the form when the blood was drawn and sent it with the sample/s to SMU.

5.5.4.1. Sample collection.

Samples were collected at the relevant study sites by the study coordinator. The collection of the samples and procedures were as follows:

- Body Mass Index (BMI) was recorded with each measure
- For the baseline measurements, the blood samples were collected at the first injectable dose. For this first dose, the peak sample was collected four to six hours post the administration of the injectable, and the trough sample was collected on the following day, 30 minutes prior to the administration of the second dose.
- The follow-up samples were collected on the relevant weeks: week 2, 4, 6, 8, 10 and 12. The peak and trough samples were collected on the same day: the sample for the trough was drawn 30 minutes prior to the injection, and the sample for the peak was drawn four to six hours after the injection.
- 2 mls of venous blood for the trough level and 2mls of venous blood for the peak level was drawn and placed in separate red top tubes.
- The study coordinator recorded the time the peak and troughs were taken, the dosages and other drugs administered to the participant, the day of therapy and the amount of drug given.
- The samples were centrifuged (4000 revs per minute for 10 minutes at 4^{o}C) prior to storage and then stored immediately in a (between 2 and 8 ^{o}C) fridge if stored for seven days or less, or in a -80 ^{o}C freezer if stored for more than a week. This was dependent on the laboratory's availability to analyse the samples.
- Creatinine results were also measured. When the test was not part of the standard of care procedures at the relevant hospital, then an extra three mls of blood was drawn (and placed in yellow top tubes) to measure this. Clinical Laboratory Services

performed these tests. However, the creatinine results conducted by the NHLS were not always accessible as stated above. This is a limitation.

- HIV testing was conducted if there was no laboratory documentation in the participants' hospital file. This occurred in accordance with the standard procedures in SA.

5.5.4.2. Pharmacokinetic calculations.

The clinical pharmacist from SMU calculated the pharmacokinetic parameters for the kanamycin and capreomycin for all participants to determine at what drug concentration toxicity was occurring.

The laboratory at SMU was prepared with all the necessary equipment. This study was entirely exploratory for correlating kinetics for kanamycin and capreomycin to hearing loss in a South African population. Pharmacokinetics in this population with kanamycin was the first of its kind. The sample analyses did not necessarily occur in 'real time'. Therefore, samples were sent weekly or twice weekly to SMU for analysis, and not immediately post sample collection. Prior to transportation, they were stored at the CHRU.

The lack of this type of study is demonstrated through a systematic review by the audiologist/researcher through database searches using various keywords. A total of 154 239 records were identified using 'Kanamycin' OR 'Capreomycin' OR 'Aminoglycosides'. Furthermore, this was refined to include 'Ototoxicity' OR 'Hearing' resulting in 3411 records. By further adding the search terms 'Pharmacokinetics' OR 'Kinetics' the number was reduced appreciably to 292. Thereafter, studies regarding 'Tuberculosis' were searched, finding nine articles. These nine articles were refined to zero when looking at the date published (six were after the development of the protocol) as well as excluding animal studies and reviews (see Figure 5.1).

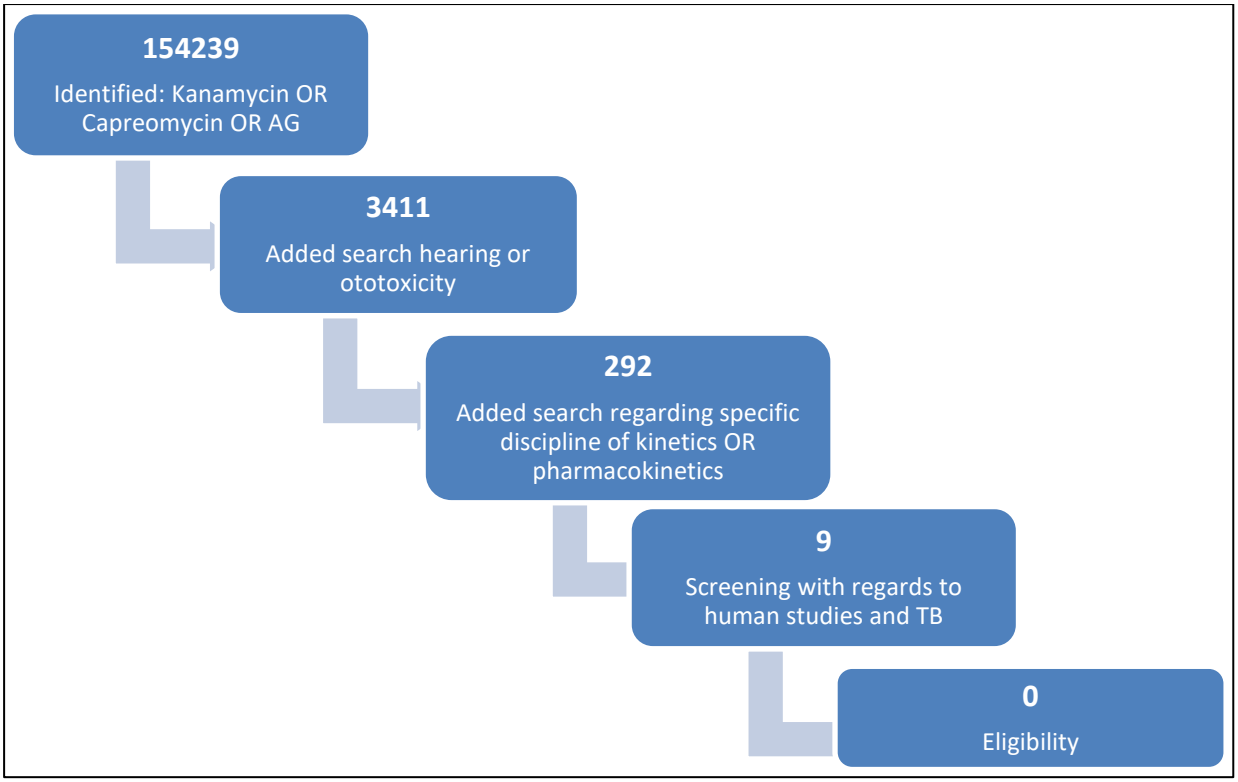

Figure 5.1. Systematic review of similar studies

The pharmacokinetic parameters were calculated by a clinical pharmacist and pharmacokinetics expert at SMU. The pharmacist recorded the amount and time of doses given, the values and times of measured drug concentrations using a pharmacokinetic graph.

The calculations of the kinetics included:

- Calculation of the elimination rate (ke) and half-life (t1/2) from peak and trough concentrations
- Determination of the C_{max} (concentration at the time the completion of the drug administration)
- Calculation of the C_{min} (concentration at the end of dosing interval)
- Calculation of the volume of distribution (Vd)
- Calculation of the Creatinine Clearance (CrCl)

The drug toxicity was subsequently correlated to trough levels.

5.5.5. Medical Treatment and Financial Arrangements

The medical management was not a specific study related procedure, however, occurred as part of the standard of care at the hospitals. The doctors, however, were involved in the study and therefore informed the study coordinator about a treatment change, such as from an adverse event, when necessary.

Furthermore, participants were not paid for the participation in the study, yet they received reimbursement for their transport and a possible day off work. This was in accordance with GCP guidelines (2006).

5.5.5.1. Treatment by the medical doctor.

- **HIV treatment***:* Each participant continued with their DR-TB treatment and HIV regimen as per the protocol at research sites. As per the NDoH (2011), all patients that were on ARV treatment at the time of the diagnosis of DR-TB continued their ARV treatment and started the MDR-TB treatment immediately. If patients were on tenofovir, lamivudine and efavirenz or nevirapine for their HIV, it was advised that the patients be stopped on tenofovir and switched to zidovudine or stavudine during the injectable phase. Then tenofovir could be re-introduced in the continuation phase of the DR-TB treatment. All the participants' HIV and DR-TB treatment thus continued as per government guidelines.
- **Adverse events**: When a participant displayed any such symptom that was unusual for patients with DR-TB, it was recorded. When a participant displayed an atypical symptom, that was likely a result of their DR-TB, it was still recorded and reviewed. The treating doctor or doctor on duty decided on the management of this patient. The adverse events in this study that was reported where nephrotoxicity. As per the protocol, when the doctors withdrew a participant from kanamycin or capreomycin and switched to another drug for DR-TB treatment, the participant was withdrawn

from the study. If the participant were however switched to a three-day kanamycin or capreomycin regimen in contrast to a five-day regimen, they would continue in the study. This would take place if there were a significant decline in hearing or kidney function, although is generally only implemented after the first three months. At SRH patients switched to capreomycin when toxicity was noted. If the nephrotoxicity continued, participants were withdrawn from kanamycin and capreomycin; if renal function deteriorated to a Glomerular Filtration Rate (GFR) < 60 then kanamycin or capreomycin. This did occur at SRH and participants were withdrawn from the study. This was the only adverse event reported.

5.5.5.2. Financial arrangements.

The participants were provided with R 150.00 for study visits where blood was drawn for study-related procedures, and hearing tests were done. This took at least 5 hours (excluding travel), and thus participants were compensated for their time and the potential of missing a day of work.

The participants were provided with R 50.00 to go to their local clinical daily and receive their kanamycin or capreomycin injections during the study, or to visit the study coordinator daily for his/her injection at either SRH or HJH. When this R 50,00 was not sufficient for transport, R 70,00 was given on an individual basis (as stipulated by the GCP guidelines and travel distance).

5.6. Ethical Considerations

Many ethical considerations were taken into account. The World Medical Association's [WMA], Declaration of Helsinki principles, guided the research (WMA, 2013). These principles were applied to this study as a means of promoting its' execution in a manner that was honest and truthful to participants and valid in implementation. The ethical

aspects considered can be categorised into four categories namely: (i) the respect for autonomy, (ii) confidentiality, and anonymity, (iii) beneficence and non-maleficence, and (iv) justice (McCormick, 2013). The manner in which these principles were reviewed and applied to this study is outlined below.

5.6.1. Respect for Autonomy

Autonomy, or respect for people, as explained by Owonikoko (2013) demands that the ability of competent participants to make their own decisions and for this to be recognised as respected, while also protecting the autonomy of the vulnerable populations by preventing the imposition of the unwanted decision.

This principle of autonomy brings forth the concept of informed consent (Owonikoko, 2013). Therefore, the GCP principle guided this informed consent procedure. Information sheets and consent forms were given to each potential participant. The study coordinator explained the consent form, in a language of choice for the patient, to ensure that the patient understood the reason of the study, what was required of him/her as well as his/her right to not consent to participate or withdraw at any time without any negative consequences. Informed consent was obtained to collect blood samples and to participate in the audiological testing. The signing of the consent form was done in accordance with GCP guidelines. The participant was given the opportunity to ask further questions or express any concerns. The study coordinator and specific investigators provided their contact details in the cover letter, should patients have felt that they required additional information. The responsibility for the protection of participants always rested with the researcher and personnel involved and never the research participants, even though they had given consent. Furthermore, participants were given the option of not participating or withdrawing from the study at any time without any repercussions or penalty.

5.6.2. Confidentiality and Anonymity

"The concept of confidentiality is closely connected with anonymity. Confidentiality is regarded as spoken or written with confidence. Anonymity, on the other hand, is one way to apply confidentiality. Anonymity in practice means that information on the identity of research" (Dube, Mhlongo & Ngulube, 2014, p.202).

All documents will remain confidential and will be stored for 15 years post-trial. It will be kept in a locked cabinet, and the database is password protected. Furthermore, participants' confidentiality was assured in that only the personnel in the hospital involved in the study, the researchers and supervisors will have access to the data. Should a participant not have completed the study, their existing data was kept safe and confidential.

In many research studies; it is the right of the participants to remain anonymous. In this study, the patients were required to give their name, as the researcher and the medical professionals needed to document the participants' progress. However, the information was not provided to anyone external to the study and names have not been mentioned in the final write-up of the results.

5.6.3. Beneficence and Non-Maleficence

"Beneficence and the twin concept of Non-Maleficence demand that subjects should not be harmed through the conduct of the study" (Owonikoko, 2013, pg. 242).

"Beneficence is defined as an act of charity, mercy, and kindness with a strong connotation of doing good to others including moral obligation. All professionals have the foundational moral imperative of doing right." (Kinsinger, 2009). In contrast, non-maleficence involves an ethical and legal duty to avoid harming others (Beauchamp & Childress, 2008).

The Helsinki principles also mention that medical research involving human participants may only be conducted if the importance of the objective outweighs the inherent

risks and burdens to the research subjects (WHO, 2001). There were few risks of the pharmacokinetic measures, mainly which included the risk of bruising from the needle entry. This was monitored, and patients displaying notable reactions that are causing significant discomfort would have been excluded from the study. Should this study lead to the future individualisation of drug therapy and dosage adjustments to reduce toxicity, it could improve the quality of life for future patients. The immediate benefit of the study involved the constant hearing testing every two weeks, and thus awareness of hearing status. This would not have otherwise been possible. The beneficence was upheld with the guiding idea, that without a hearing loss or with a lesser degree of hearing loss, patients are not restricted or not *as* restricted from many job applications and thus not limited to state grants, which would place the government under financial burden.

Furthermore, with regards to non-maleficence, in all research involving the investigation of human participants, ethical approval is required in order to ensure the psychological and physical safety of each person. The need to conduct research ethically is vital to every research project and is essential to obtain credibility of the collected data (O'Leary, 2004). Therefore, firstly, permission to conduct this study was obtained from the University of the Witwatersrand's Human Research Ethics Committee (Medical) (Appendix A). Subsequently, in addition, permission to conduct the study at the hospitals was obtained from the relevant hospitals CEOs. Lastly, permission from the individual patients participating was obtained. No change to the protocol took place without consideration and approval by the committee (see Appendices A and B).

The research team did everything in their power to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of the participants participating in the study. The research and data collection were conducted by individuals with the appropriate scientific training and qualifications.

5.6.4. Justice

Justice in research demands that all participants or clinical subjects be treated fairly (Owonikoko, 2013). At the conclusion of the study, participants entered into the study were entitled to be informed about the outcome of the study.

Daniels (2004) further discusses the principles of veracity as part of ethical research in human participants. This principle would refer to truthfulness. Deception can take many forms: intentional lying or non-disclosure of information or partial disclosure information. Nothing was hidden from the participants.

After the three months of data collection or dropout from the study, participants were referred to the hospitals' audiology department to continue monitoring of hearing, and for the management of possible hearing loss post DR-TB treatment (i.e. with hearing aids). Should HJH or SRH not have been in the participants' catchment area, the department referred the participant to the relevant hospital. The participants were also fairly provided with money for their transport to the clinic/hospital for study-related procedures when they were not treated as inpatients. R 150.00 was provided for study visits where blood was drawn for study-related procedures, and hearing tests were done. This could take a day, and thus participants were compensated for missing a day of work. R 50.00 was provided for the participant's transport to go to their local clinical daily and receive their kanamycin/capreomycin injection during the study. Should this not have covered the transport, it was discussed on an individual basis and arrangements were made to increase this amount to R 70.00.

5.7. Reliability, Validity, and Bias of Data

Reliability and validity are the key indicators of the quality of a measuring instrument (Kimberlin & Winterstein, 2008). "In healthcare and social science research, many of the variables of interest and outcomes that are important are abstract concepts known as

theoretical constructs. Using tests or instruments that are valid and reliable to measure such constructs is a crucial component of research quality". (Kimberlin & Winterstein, 2008, p 2277).

5.7.1. Reliability

Reliability is a measure of precision or accuracy of an instrument (Roberts, Priest & Traynor, 2006; Heale & Twycross, 2015) and refers to the consistency of a measure (Gravetter & Forzano, 2011). There are different ways of estimating the reliability of any measure, which include the evaluation of the stability of the measures (test-retest reliability), the equivalence of sets of items from the same test (internal consistency) or different observers scoring a behaviour or event using the same instrument (interrater reliability) (Kimberlin & Winterstein, 2008).

5.7.1.1. Stability or test-retest reliability.

Stability is tested using test-retest and parallel or alternate-form reliability testing (LoBiondo & Haber, 2014). Test-retest reliability is assessed when an instrument is given to the same participants more than once under similar circumstances. A statistical comparison is made between participant's test scores for each of the times they have completed it. This provides an indication of the reliability of the instrument (LoBiondo & Haber, 2014).

Test-retest reliability was obtained when training the study coordinator. The study coordinator and an independent audiologist conducted PTA on the researcher. Testing was done within the same month, and responses were required to be within 5 dB of each other to ensure reliable testing procedures. This took place primarily to ensure interrater reliability, but also to ensure the stability and repeatability of the test. When results with PTA were within 5 dB, then the results were considered stable, and the efficiency of the study coordinator was adequate. Testing by the study coordinator and audiologist could not repeatedly be done on participants as they tired quickly.

Furthermore, the test-retest reliability of the audiological measures has undergone previous investigation during the development of the actual procedures. Franklin, McCoy, Martin & Lonsbury-Martin, (1992) investigated test-retest reliability of DPOAEs and concluded that the consistency of the measures was excellent. Furthermore, test-retest reliability for PTA was also shown to be excellent up to 12 kHz, yet with slightly more variability between 14 kHz and 16 kHz (Schmuziger, Probst & Smurzynski, 2004). However, Ahmed et al. (2001) showed test-retest reliability with UHFA was as reliable as the conventional audiometry.

With regards to the pharmacokinetics, test-retest reliability was established with the mass spectrometer prior to the collection of participant samples. Serum levels with kanamycin and capreomycin were repeatedly tested to confer consistent results. This is explained further in 5.6.2.3.

5.7.1.2. Equivalence or internal consistency.

Internal consistency provides an estimate of the equivalence of sets of items from the same test, for example, a set of questions aimed at assessing the quality of life or disease severity) (Kimberlin & Winterstein, 2008). In this study, the audiological tests, in combination, aimed to assess ototoxicity; a protocol devised from consideration of various sources.

The coefficient of internal consistency provides an estimate of the reliability of measurement and assumes that items measuring the same construct should correlate (Kimberlin & Winterstein, 2008). In split-half reliability, the results of a test, or instrument, are divided in half. Correlations are calculated comparing both halves. Strong correlations indicate high reliability, while weak correlations indicate the instrument may not be reliable (LoBiondo & Haber, 2014).

The reliability of the hearing tests was assessed with split-half reliability. The DPOAEs and PTA did show correlation. This ensued by looking at the frequencies in the PTA in relation to the frequencies of the DPOAEs that showed the most change through the various weeks. Although the greater change in the hearing was noticed on the DPOAEs, this was to be expected as DPOAEs are more sensitive. Yet, the correlation was not always noticed, which could indicate shortfalls in the reliability of the measures (Chapter 6 and 7).

5.7.1.3. Interrater reliability.

Interrater reliability, or interobserver agreement, establishes the equivalence of ratings obtained with an instrument when used by different observers (Kimberlin & Winterstein, 2008). This test includes a process for qualitatively determining the level of agreement between two or more observers. This is used to assess the degree to which different raters/observers give consistent estimates of the same phenomenon (Zanarini, Frankenburg, Chauncey & Gunderson, 1987).

As there was only one study coordinator, interrater reliability was not assessed during the study. Although at times, the researcher did conduct audiometry, it was not conducted at the same time on the same participant. This would have been difficult as the participants were ill and tired easily. They could not return the following day for the ‘re-test’, and the changes noted between the weeks were an indication of ototoxicity and not poor interrater reliability (when the researcher and study coordinator conducted testing on the same participant at different weeks). However, the researcher viewed the results, and inconsistencies were noted. No notable errors with testing were identified, and so testing was not repeated.

5.7.2. Validity

Validity is a measure of accuracy (Roberts et al., 2006) and refers to whether the study was able to scientifically answer the questions that it was intended to answer (Gravetter & Forzano, 2011). Validity requires a reliable instrument. However, the instrument can be

reliable without being valid (Kimberlin & Winterstein, 2008). Validity can be assessed by examining the internal and external validity, which encompass various aspects (Yu, 2017). Test validity is discussed further due to its specific relevance to this current study, followed by the inclusion of the pilot study to ensure the validity further.

5.7.2.1. Internal validity.

"Internal validity refers specifically to whether an experimental treatment/condition makes a difference in the outcome or not, and whether there is sufficient evidence to substantiate the claim" (Yu, 2017, p.1). It is concerned with correctly concluding that an independent variable is responsible for the variation of the dependent variable and can be affected when research participants try to figure out what is expected of them and perform accordingly (Kirk, 2009).

Thus, in this study, the *internal validity* would refer to whether the pharmacokinetic factors were responsible for the lack of change of hearing the status of patients on kanamycin and capreomycin for DR-TB. Internal validity addresses whether an observation co-variation or experimental condition should be considered a causal relationship (Yu, 2017).

Internal validity can be affected when research involves individuals, because of demand characteristics, which is when participants are told to perform a task; they try to figure out what is expected of them and perform accordingly. There were participant predisposition effects (such as genetic influences of susceptibility to aminoglycoside toxicity) as well as experimenter bias (Kirk, 2009). Because some of the measures were objective, such as with the audiological measures including tympanograms and OAEs as well as pharmacological testing, the participants and experimenter had no control over the outcome of these measures, which strengthened the internal validity.

There are various threats to internal validity which were noted, and subsequently, considerations were implemented to minimise these threats:

- **History**: the specific events which occur between the first and second measurement (Yu, 2017). In this study, it could apply to the participant's activities between the study related procedures. It was difficult to track the medications that participants may or may not have taken between the study visits. However, in-depth counselling was conducted to explain the importance of complying with all study-related procedures. Furthermore, for the outpatients, the clinic sisters were required to sign when the participant received the injectable, and the participant was further required to complete a drug diary to track drugs ingested. However, it must be noted that there may have been deviations that were not reported. Furthermore, it is possible that participants were exposed to noise in between the study visits which could have affected the audiological outcomes.
- **Maturation**: the processes within subjects which act as a function of the passage of time (Yu, 2017). As this study only took place over a maximum of 12 weeks for each participant, maturation was not affected.
- **Testing**: the effects of taking a test on the outcomes of taking a second test. In other words, the pre-test becomes a form of "treatment" (Yu, 2017). Learning effects (practice or carryover effects) or experimental fatigue (physical and mental fatigue of participants) were considered (Savage & Waldman, 2008). The blood sampling and DPOAEs were objective measures, and thus the validity was not affected. With regards to PTA, the effects of the multiple tests could affect the validity, however, as tones were presented inconsistently, the participant could not ‘learn’ the response.
- **Instrumentation**: the changes in the instrument, observers, or scorers who may produce changes in outcomes (Yu, 2017). This could include the personal

characteristics of the researcher, which influenced the choices made during a study; and non-verbal cues that the researcher gave out that may have influenced the behaviour and responses of participants. However, the study coordinator was instructed to maintain neutral throughout the audiology testing as well as a collection of information during the case report forms.

- **Experimental mortality**: the loss of subjects this current study, where the sample size was smaller than expected, and so the validity of the outcomes need to be considered further in a larger sample. However, this study aimed to assess feasibility, and this aspect of validity impacted the feasibility. (Yu, 2017).

5.7.2.2. External validity.

External validity describes whether the causal relationship discovered can be generalised to other people, times and contexts (Rothwell, 2005). Threats to external validity relevant to this current study can include population and ecological validity.

Population validity refers to the extent to which the findings can be generalised form the sample group towards a more substantial target population (Onwuegbuzie, 2000). As there are three outpatient treatment sites for DR-TB (involving smear negative DR-TB patients), and two of the three were included in this study, the researcher could assume that the accessible population is representative of the target population. Data was collected from all the participants who consented and fitted the inclusion and exclusion criteria. These criteria were determined to exclude variables that could contribute to hearing loss unrelated to the study aims. Although the sample was small, it should represent other patients receiving treatment for DR-TB in similar treatment regimens.

Ecological validity refers to the extent to which the findings from a given study can be generalised across settings, conditions, variables, and contexts (Onwuegbuzie, 2000). This could influence the study, as the data and final results were dependent on the setting and

location it which they were obtained. The researcher will not attempt to minimise this effect, as the aim of the study is focused on this specific context, and on feasibility. Future research should aim to generalise to a different setting where DR-TB is treated.

5.7.2.3. Test validity.

Validity is defined as the extent to which a concept is measured accurately in a quantitative study. Validity is defined as the extent to which a concept is measured accurately in a quantitative study.

Test validity: This category determines whether the instrument adequately covers all the content that it should with respect to the variable content

Content validity examines whether the instrument adequately covers all content that is should with respect to the variable (Heale & Twycross, 2015). This can be considered with audiological and pharmacological measures:

- **Audiological Measures**: Hearing tests were conducted using PTA and DPOAEs. High-frequency measures were conducted explicitly to detect early changes in hearing levels and cochlear functioning. Using both these measures allowed for the detection of sub-clinical changes to cochlear functioning, such as with DPOAEs as well as early changes with hearing levels as testing included up to 16 kHz with pure tones. Measures such as otoscopy, tympanometry, and noise monitoring ensured that the PTA and DPOAEs revealed valid data, and outer/middle ear status, as well as noise levels, were not affecting the results.
- **Pharmacological Measures**: The instrument, namely the mass spectrometer, was chosen to detect the kanamycin and capreomycin levels in the serum. This occurred after the investigation of other methods, such as the use of an HPLC, which was not sensitive enough.

Construct Validity refers to whether one can draw inferences about test scores related to the content being studied; the extent to which a research instrument (or tool) measures the intended construct.

- **Audiological Procedures**: The audiological tests used in this study have been validated. ASHA recommends the use of high-frequency PTA and DPOAEs to detect changes in hearing resulting from ototoxicity (ASHA, 1994). Thus, the validity of these measures has already been established. Also, the signal to noise ratio (SNR) assisted in determining validity. Those with SNRs below 3 dB were automatically discarded and viewed as a missing response. SNRs of 3 to 6 dB (inclusive) was initially planned to be analysed. However, it only included three readings of various participants during several weeks at different frequencies. As there were only three readings at a 3-5 dB SNR, with the majority at 6 dB or above, the results of the 6 dB SNR were utilised to ensure reliability and validity of the results. Additionally, two DPOAE readings obtained for each measure, with the assistance of the validity of the measures. The DP responses were averaged out, and then the single average was used.
- **Laboratory Procedures**: The validity of the detection of the kanamycin and capreomycin levels in the serum was validated by the biochemist before the test. The following procedures were followed for the validation for data analysis:

  Sample Preparation: The samples were centrifuged (4000 revs per minute for 10 minutes at 4^{o} C) prior to storage and then stored immediately in a (between 2 and 8^{o} C) fridge if stored for seven days or less, or in a -80^{o} C freezer if stored for more than a week. This was dependent on the laboratory's availability to analyse the samples.

  Preparation of Standard Curve for Calibration and Sample Extraction: A stock solution of kanamycin (100 ppm) was prepared. From this secondary standard

was prepared (10 ppm) and used to fortify the following levels in blank serum; 1.69, 4.99, 9.99, 16.65, 23.30, 33.30 µg/ml.

- The sample extraction procedure involved deproteinising the samples using organic solvents. Three millilitres of acetonitrile (Merck or Sigma, grade) was added to 1 ml of serum. The samples were briefly vortexed and were then centrifuged using Beckman Coulter (Allegra^{TM} X-22) centrifuge at 5000 g for 20 min at 4 ^{0}C. The supernatants were collected immediately; filtered using nylon syringe filters (0.22 µm, 13 mm) into a 2 ml vial, and subjected to LC-MS/MS analysis.

Chromatography and detection

- ASCIEX 3200Qtrap (SCIEX) mass spectrometer with turbo spray source was operated in both positive using an Agilent 1200 series binary pump system. Multiple reaction monitoring (MRM) was used with 5000 V at 500° C source temperature. The curtain gas was set to 20 psi, with GS1 and GS2 both at 40 psi. The CAD gas was set to 8 psi with the collision energy and declustering potential (DP) set to compound specific optimisation conditions (refer to MRM table). Chromatographic separation was achieved in a 14-minute gradient run using 350 µℓ/min flow rate on a Zorbax Extend C18, 2.1 x 100 mm, 3.5 µm particle size, 100 x 2.00 mm (Agilent) column at 40°C. The mobile phases were; A –3.2 mM ammonium formate, with 50 mM Heptafluorobutyric acid (Sigma Aldrich) in water (H_2O); B – 0.1% formic acid in acetonitrile. Column conditions were kept at 95% A for the first minute, then gradually increased to 98% B over 2 minutes, and kept at 98% B for another 7 minutes, then returned to initial gradient conditions. The ion spectra were acquired by injecting 20

µL of the sample on the autosampler, and quantification was performed by comparing the peak areas with authentic matrix-matched standards of each compound as listed in Table 5.15.

Table 5.15

Multiple Reaction Monitoring for kanamycin and capreomycin

Compound	Precursor mass (m/z)	Production mass (m/z)	Declustering potential (Volts)	Collision energy (Volts)
Kanamycin MRM1	485.300	163.1	41	35
Kanamycin MRM2	485.300	324.4	41	25
Capreomycin IA MRM1	669.360	98.3	111	91
Capreomycin IA MRM2	669.360	507.2	111	37
Capreomycin IA MRM3	669.360	127.1	111	95
Capreomycin IB MRM1	653.367	98.1	126	91
Capreomycin IB MRM2	653.367	491.3	126	35
Capreomycin IB MRM3	653.367	70.0	126	101

Criterion validity examines the ability of a measure to predict a variable that is designated as a criterion (Epstein, Preston, Stewart, & Shaham, 2006). This looks at the relationship between a test score and an outcome. Because much of the audiological testing was objective, there was no room for individual interpretation and subjective findings, which ensured the validity of the tests, in looking at the cochlear functioning. The equipment is calibrated annually which ensures that the results were indeed valid, and the equipment was working efficiently.

5.7.2.4. Pilot study.

Pilot tests can be viewed as ‘dress rehearsals’ of the full operation, in this case, a study with a larger population. It is implemented to determine whether existing problems can be addressed effectively before putting the entire production to play (Lavrakas, 2008).

As this data collection process had never been applied in practice, a pilot test was conducted to establish any possible issues that could arise. The purpose of this was to ensure that the data collection process and equipment was sufficient and contained every aspect that the researcher wanted to address in the study. By performing a pilot test, the researcher was able to highlight any shortcomings, mistakes, unnecessary or insufficient aspects and to correct and adjust the data collection sheet accordingly. The pilot test was conducted once the protocol received ethical clearance. It was part of the data collection process and involved the first five participants. After the first five participants, it was decided that the protocol could continue unchanged and these participants were included in the main study.

5.7.3. Bias

Bias can be defined as any systematic error with a tendency for selectivity or influence, meaning that the research findings deviate from the 'true findings'. Bias can occur at any stage of the research (Pannucci & Wilkins, 2010).

Sampling bias occurs when the sample is collected in such a way that some members of the intended population are less likely to be included than others. This effect was minimised through the means of using the same protocol in the various contexts. Purposive sampling was also done to include all participants that would qualify according to inclusion and exclusion criteria.

Analytical bias results from differences in methods and techniques used to evaluate the results. All results were evaluated using the same method and technique to capture and analyse data.

5.8. Data Management and Analysis

All data was captured and managed as per procedures at the CHRU at Wits Health Consortium. All participants were given a study number generated by a specified database. Thus, all data could be synchronised.

The quality assurance of data was ensured via various aspects. In the design phase of the study, the project aims guided the development of the case report forms for the collection of data. This took place to ensure quality (rather than quantity) of data as well to ensure all the steps of the data collection could be adhered to (Needham et al., 2009). These data collection forms were drawn up in collaboration with a skilled data management team at CHRU.

In the data collection phase, standardised data collection forms were utilised for all the participants (Needham et al., 2009). These data collection forms adhered to the GCP guidelines and layout of the general CHRU data collection forms. This was done to ensure that the study coordinator and data capturers were familiar with the forms to ensure the correct capturing of data.

Furthermore, the data management included comprehensive staff training, and a well-designed database can help maximise the quality of the data (Needham et al., 2009). The researcher conducted the staff training (for the study coordinator and data capturers). The training included the clear explanation of specified defined data elements. Also, the data collection forms were reviewed by data manager at CHRU to ensure a quality according to their standards. Additionally, the database was designed by the database design IT employee at CHRU. The data capturer captured the data monthly on this specified secure database.

Quality assurance reviews of both collection and entry and system-based controls reduce the likelihood of error (Needham et al., 2009). The data manager assisted with the review of captured data onto the database, while the researcher reviewed the paper-based data

as well. This was to ensure that missing data should be identified quickly and corrected with system-based controls to minimise the missing data. This missing data, however, was not always recovered due to the nature of the outpatient study design, which was a shortfall in the quality assurance plan in the current study.

Finally, in the data analysis phase, sensitivity analysis aided in managing and understanding the effects of missing data and outliers (Needham et al., 2009). Due to the small sample size, the data were analysed descriptively using tables, graphs, means, medians, and standard deviations.

All data used Microsoft Excel as an analysis tool. Audiological results were analysed according to change from the baseline at the various frequencies. The mean values were considered for each ear separately.

The pharmacokinetic results analysed the results in relation to the hearing levels, yet for both ears combined as well, in comparison to the ears separately. The mean peak and trough values were analysed for kanamycin and capreomycin separately, throughout the weeks, as well as the half-lives, volumes of distribution and dosages where possible. The mean creatinine values were used.

5.9. Conclusion

This chapter detailed the method of this study, including the design, sample selected and the research team. It then described the data collection process including the forms and equipment used as well as procedures. Ethical guidelines were discussed, as well as validity and reliability measures. Lastly, data analysis procedures were discussed which were used to analyse the data that are presented in Chapter 6.

Chapter 6: Results

This chapter describes the findings of the study in a clinically descriptive manner according to the aims of the study. Firstly, the audiological results of the study have been described, followed by the pharmacokinetic results, and subsequently the relationship between the audiology and pharmacokinetics. The chapter concludes with the main aim, namely the feasibility component.

6.1. Audiological Results

This section addresses the following sub-aims of this study:

To determine the changes in hearing levels in patients undergoing treatment with kanamycin and capreomycin for DR-TB.

- To determine the prevalence of abnormal findings on baseline hearing assessments.
- To determine the change in hearing levels from baseline.

These sub-aims will be addressed by discussing PTA, and subsequently the DPOAEs. Each ear will be described as separate entities initially, and then correlated after. The various frequency ranges will be described.

6.1.1. Pure Tone Audiometry

The results are presented in three frequency ranges; namely low frequencies, high frequencies and ultra-high frequencies. Low frequencies are, for the purpose of this study, 0.25 kHz until and including 2 kHz, whilst high frequencies are described as frequencies between and including 3 kHz and 8 kHz as measured on the conventional audiogram (Seddon et al., 2012). Ultra-high frequencies in this current study are specified as 9 kHz until and including 16 kHz.

The mean thresholds for all participants were calculated at each frequency for the seven study visits (T0 - T6) and are presented in the three frequency ranges for the right ear (Table 6.1) and the left ear (Table 6.2).

In addition, the hearing loss for all participants is graded according to the existing adult grading scales for hearing loss, namely the TUNE and CTCAE scales. The ASHA (1994) criteria are also used to describe the hearing loss, however, is not considered a grading scale.

The CTCAE, although designed for children, has adult applications, yet only grades up to 8 kHz. The CTCAE consists of four grades, from a threshold shift of 15-25 dB from baseline at two or more adjacent frequencies in at least one ear (grade 1), a threshold shift of greater than 25 dB to 90 dB in at least two adjacent frequencies in at least one ear (grade 2), the requirement of intervention such as 25-90 dB, averaged at three adjacent test frequencies in at least one ear (grade 3) to the final grade 4 of requiring a cochlear implant (Durrant, et al, 2009). The TUNE scale, in contrast, grades up to 12.5 kHz, but also grades up to grade 4. It, however, consists of grade 0 indicating no hearing loss, with grade 4 being a hearing level ≥70 dB at 1 kHz to 4 kHz. Grades 1 and grade two contain an ‘a’ and ‘b’ which both discuss the same in decibel loss in the respective grade, however, include different frequencies. Grade 1 indicates a change of greater than 10 dB, with grade 2 indicating a shift of more than 20 dB. The ‘a’ for both grades refers to frequencies between 8 kHz to 12.5 kHz, with the ‘b’ indicating a change from 1 kHz to 4 kHz. Subsequently, grade 3 indicates a hearing level of ≥ 35 dB at 1 kHz to 4 kHz (Theunissen et al., 2014). The ASHA criteria, on the other hand, define a significant change from baseline, yet does not differentiate the frequencies (Konrad-Martin et al., 2005).

6.1.1.1. Low frequencies.

The low frequencies are from 0.25 kHz to2 kHz, inclusive. In both ears, minimal changes in hearing thresholds occurred across the study visits as the mean thresholds were all between 16 dB and 25 dB, showing a slight hearing impairment (ASHA, 2015). The right ears showed its most significant change at 0.5 kHz of 7 dB where the left ears largest threshold change was at 2 kHz of 3 dB. However, both ears showed no clinically significant change at the low frequencies and no ototoxicity was observed (Tables 6.1 and 6.2). This loss of hearing does not fit the criteria to be graded.

6.1.1.2. High frequencies.

The higher frequencies in the conventional audiogram are from 3 kHz to 8 kHz. In both ears, it is evident that hearing thresholds deteriorated over time from T0 to T6. See Tables 6.1 and 6.2.

As participants were required to respond behaviourally, results could not always be obtained. When participants were tired and sickly, they did not want to and/or could not participate reliably. This occurred three times; twice at T2 and once at T4. The PTA results were not conducted at 9 kHz for one participant at T1, and so all the other participants mean results were used. In the right ear, the significant changes were observed at 6 kHz and 8 kHz from T0 to T6 (10 dB or greater mean change) (Table 6.1). At 6 kHz and 8 kHz, the hearing can be classified as a mild hearing loss (ASHA, 2015), as well as it can be graded according to the TUNE scale and acknowledged as significant according to the ASHA criteria.

The left ear, in contrast, shows a significant shift at only 8 kHz of 10 dB. This can be graded as a grade 1a according to the TUNE grading scale, which is a threshold shift ≥ 10 dB at 8 kHz to 12.5 kHz. It does not fit the criteria for a grade on the CTCAE scale nor the ASHA system (Table 6.2).

6.1.1.3. Ultra-high frequencies.

Ultra-high frequencies in this study are considered from and including 9 kHz up to and including 16 kHz. It is important to note that at 16 kHz specifically, a limitation was observed, as the audiometer was only able to record a hearing loss of 55 dB and better (PATH manual, 2015). During data collection, for participants with a threshold of ≥ 56 dB, the results were recorded as *no response*. However, for statistical and graphical reasons, these participants' thresholds were recorded at 55 dB, despite that assumption that their thresholds were ≥ 56 dB. Although we know that their hearing loss is greater, we cannot assume at what dB level the threshold is at, and so a 55 dB was recorded for these participants. As will be observed below, 16 kHz showed a lesser hearing loss than the other ultra-high frequencies.

In both ears, the greatest change in hearing levels in noticed in these UHFs above 8 kHz: the greatest change in hearing was at 11.2 kHz bilaterally.

In the right ears, the smallest change was noted at 16 kHz of 11 dB; however, this is possible a skewed result as those with no responses were still recorded at 55 dB. All the ultra-high frequencies in the right ear showed significant change, while only 9 kHz, 10 kHz, and 11.2 kHz showed a significant change in the left ears Tables (6.1. and 6.2).

Table 6.1

Mean Pure-Tone Thresholds: Right Ear

Frequencies (kHz)		**Mean Pure-Tone Thresholds (dB) (right ear)**						
		T0 (n = 22)	**T1** (n = 15)	**T2** (n = 9)	**T3** (n = 9)	**T4** (n = 9)	**T5** (n = 7)	**T6** (n = 6)
Low frequencies	**0.25**	19.77	21.00	20.56	21.00	26.11	20.71	24.17
	0.5	21.36	21.67	22.78	22.78	25.00	22.14	27.50
	1	18.64	19.33	18.89	18.89	22.22	20.71	21.67
	2	14.55	13.00	17.22	15.56	16.11	16.43	19.17
High frequencies	**3**	17.73	17.67	21.11	21.11	22.22	20.00	20.83
(* Grade 1a, #)	**4**	15.00	17.33	16.11	18.89	20.00	17.14	17.50
	6	15.91	22.00	20.00	27.22	28.33	20.00	25.83
	8	20.45	23.67	26.67	26.11	27.78	30.71	32.50
Ultrahigh frequencies	**9**	19.09	22.14	23.89	28.33	32.78	32.86	35.83
(* Grade 1a, #)	**10**	19.55	21.00	23.33	30.00	33.89	33.57	39.17
	11.2	20.68	28.00	31.67	33.89	38.89	39.29	46.67
	12.5	29.55	35.67	41.11	42.22	46.67	46.43	50.83
	14	36.14	43.33	49.44	50.00	55.56	48.57	56.67
	16	35.91	42.67	45.00	46.11	46.11	42.86	46.67

Note: *TUNE: Significant change from T0 (baseline) to T6, +CTCAE: Significant change from T0 (baseline) to T6, # ASHA: Significant change from T0 (baseline) to T6

Table 6.2

Mean Pure-Tone Thresholds: Left Ear

Frequencies (kHz)		**Mean Pure-Tone Thresholds (dB) (left ear)**						
		T0 (n = 22)	**T1** (n = 15)	**T2** (n = 9)	**T3** (n = 9)	**T4** (n = 9)	**T5** (n = 7)	**T6** (n = 6)
Low frequencies	**0.25**	19.77	20.67	19.44	20.00	20.56	17.86	21.67
	0.5	23.64	21.33	17.78	22.78	24.44	21.43	24.17
	1	22.27	20.67	19.44	20.00	22.22	19.29	21.67
	2	16.36	15.67	17.78	16.67	17.22	15.00	19.17
High frequencies	**3**	18.18	18.00	20.56	20.56	18.89	18.57	19.17
(* Grade 1a)	**4**	16.14	19.67	18.33	21.11	25.00	20.71	21.67
	6	19.55	21.33	20.00	24.44	30.00	24.29	24.17
	8	21.82	24.67	23.89	30.56	31.11	33.57	31.67
Ultrahigh frequencies	**9**	17.73	21.43	23.33	29.44	27.78	35.71	30.83
(* Grade 1a. #)	**10**	17.05	21.67	23.33	30.00	30.00	37.86	30.83
	11.2	22.27	33.33	27.22	36.11	36.11	35.71	35.83
	12.5	26.14	30.33	32.22	37.78	35.56	37.14	32.50
	14	32.27	37.00	41.67	43.33	43.33	40.71	34.17
	16	30.00	30.67	43.33	40.00	41.11	35.71	39.17

Note: *TUNE: Significant change from T0 (baseline) to T6, +CTCAE: Significant change from T0 (baseline) to T6, # ASHA: Significant change from T0 (baseline) to T6

6.1.1.4. Summary of Pure Tone Audiometry.

In conclusion, the basic audiological pattern of hearing loss was similar bilaterally, in that the low frequencies were affected minimally, 8 kHz in the high frequencies was most affected, and 11.2 kHz in the ultra-high frequencies was most affected. However, the right ears displayed a more clinically significant hearing loss than the left ears according to the PTA.

6.1.2. Distortion Product Otoacoustic Emissions

There are several DPOAE results missing for participants, due to equipment issues and SNR variations. This occurred four times in total. Yet, in another two instances, only some DPOAE results were missing at some frequencies in the right ears. This occurred at T1 where the DPOAE results were missing in 6 kHz, 8 kHz and 12 kHz in the right ear, as well as at T5, where the right ears DPOAE results were missing at 6 kHz, 8 kHz, and 10 kHz. Repeat readings were not obtained at these frequencies and thus discarded.

Those with SNRs below 3 dB were discarded automatically and viewed as a missing response. SNRs of 3 - 5 dB (inclusive) was planned initially to be analysed. However, it only included two readings of various participants during various weeks at different frequencies. As there were only two readings at a 3-5 dB SNR, with the majority at 6 dB or above, the results of the 6 dB SNR were utilised.

DPOAEs were not split with the frequency ranges when analysed, as were the pure tone results. This is due to the fact that fewer frequencies were tested using the DPOAEs; from 2 kHz to 12 kHz, with six frequencies in total bilaterally. Two DPOAE readings were obtained for each measure. The DP responses were averaged out, and then the single average was used.

6.1.2.1. Low to ultra-high frequencies.

In both ears (Tables 6.3 and 6.4), DPOAE responses were recorded from baseline (T0) to week 12 (T6). Significant changes of 6 dB or greater, from baseline to week 12, were noted at all frequencies bilaterally, except for 12 kHz in the left ear, where a change of 5 dB was noted.

Table 6.3

Distortion Product Otoacoustic Emission Mean Thresholds: Right Ear

Frequencies (kHz)		DPOAE Thresholds (dB) (right ear) (SNR=6 dB+)						
		T0 (n = 22)	**T1** (n = 15)	**T2** (n = 9)	**T3** (n = 9)	**T4** (n = 9)	**T5** (n = 7)	**T6** (n = 6)
Low frequency	**2***	10.76	5.71	2.80	3.06	2.10	1.29	-1.92
High frequencies	**4***	8.17	2.67	2.40	0.22	-2.70	-0.71	-0.67
	6*	6.00	-2.32	-2.55	-5.61	-6.50	-3.00	-7.50
	8*	2.21	-5.50	-5.25	-6.00	-8.28	-7.83	-10.50
Ultrahigh	**10***	4.52	-1.17	-3.20	-8.28	-8.75	-7.83	-12.00
frequencies	**12***	-5.45	-9.60	-5.50	-13.44	-12.94	-14.50	-15.75

Note: *significant change from T0 (baseline) to T6

Table 6.4

Distortion Product Otoacoustic Emission Mean Thresholds: Left Ear

Frequencies (kHz)		DPOAE Thresholds (dB) (left ear)(SNR=6 dB+)						
		T0 (n = 22)	**T1** (n = 15)	**T2** (n = 9)	**T3** (n = 9)	**T4** (n = 9)	**T5** (n = 7)	**T6** (n = 6)
Low frequency	**2***	5.33	3.04	1.50	1.11	0.56	1.50	-3.00
High	**4***	2.21	-3.08	-1.55	-2.44	-6.75	-3.21	-7.58
frequencies	**6***	0.67	-4.08	-1.40	-3.17	-7.25	-4.07	-8.83
	8*	-2.07	-7.33	-4.40	-6.78	-7.80	-9.43	-9.17
Ultrahigh	**10***	1.40	-6.67	-5.60	-7.67	-9.10	-9.00	-8.67
frequencies	**12**	-4.68	-9.18	-6.39	-10.67	-10.11	-5.50	-10.00

Note: *significant change from T0 (baseline) to T6

6.1.2.2. Summary of DPOAEs.

In summary, the right ear, as for PTA, on average showed a greater shift when compared to the left ear. The ears showed the greatest loss in amplitude in different frequencies as well. However, both ears showed reduced amplitude over time in all frequencies (except at 12 kHz in the left ear).

6.1.3. Comparison of Pure Tone Audiometry and DPOAEs

Overall, PTA showed decreased hearing acuity while the DPOAEs showed reduced OHC function in the cochlea from baseline to week 12. Both PTA and the DPOAEs showed that the right ear displayed greater loss of hearing and cochlear function respectively than the left ears. However, PTA did not identify a significant loss of hearing at 2 kHz, where, the DPOAEs did. The high-frequency hearing loss identified is in accordance with literature, where DPOAEs are more sensitive than PTA (Guthrie, 2008). The PTA showed the most significant shift at 11.2 kHz, where the DPOAEs showed the most significant shift at 10 kHz. This does PTA does not correlate entirely with the DPOAEs. However, 11.2 kHz was not measured with the DPOAES due to limits of the DPOAE machine, and thus this frequency could not be compared with a DPOAE response. In the left ear, 4 kHz displayed the greatest change with the DPOAEs, which does not correlate to the 11.2 kHz with the PTA.

6.1.4. Symmetry of Hearing Loss

For this current study, symmetry was defined as similarity in dB responses within 10 dB between ears, based on the combination of various opinions (Djalilian, 2015; Mabgham, 1991; Sabini, 2000; Urben, Benninger & Gibbons, 1999).

Sabini (2000) considered the asymmetrical hearing loss as 10 dB or greater in 2 consecutive frequencies or 15 dB in any one frequency between 0.25 and 6 kHz (Sabini, 2000). Djalilian (2015) defined asymmetric hearing loss as a difference of 15 dB between the

right and left ears at three contiguous frequencies while Pittman and Stelmachowicz (2003) describe asymmetric losses as more than 20 dB at one or more test frequencies. Another approach by Mangham (1991) of asymmetry analysed it as an average interaural difference of greater than 10 dB at 1, 2, 4, and 8 kHz. Urben et al. (1999) defined asymmetrical hearing loss as asymmetries of 10 dB or greater at two or more frequencies or 15 dB or greater at one frequency.

No clear-cut definition has been found for asymmetry, specifically for ototoxicity that includes ultra-high frequencies. As 10 dB for PTA (Konrad-Martin et al., 2005) and 6 dB for DPOAEs (Roede et al., 1993) was considered a significant change in this current study, it was also used to describe significant asymmetries for the specified individual frequencies. Hearing loss resulting from aminoglycosides is symmetrical (Harris & Heinze, 2015).

The symmetry of the ears with PTA and DPOAEs are presented in Tables 6.5 and 6.6 respectively. The left ears' decibel response for both PTA and DPOAEs was subtracted from the right ears' response at each frequency for kanamycin and capreomycin.

The asymmetry differs on PTA and DPOAEs. Asymmetry was noticed on visits T1, T4 and T6 with PTA, yet on visits T0, T1, T5 and T6 with DPOAEs.

Table 6.5

Symmetry of PTA: *Right Ear dB Response (MEAN) Minus Left Ear dB Response (MEAN)*

kHz	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
3 kHz	0	0	1	1	3	1	0
4 kHz	-1	-2	-2	-2	-5	-4	-4
6 kHz	-4	1	0	3	-2	-4	1
8 kHz	-1	-1	3	-4	-3	-3	1
10 kHz	3	-1	0	0	4	-4	7
11.2 kHz	-2	-5	4	-2	3	-2	9
12.5 kHz	3	5	9	4	11*	9	16*
14 kHz	4	6	8	7	12*	8	19*
16 kHz	6	12*	2	6	5	7	6

Note: *Asymmetry (Difference of ≥10 dB)

Table 6.6

Symmetry of Distortion Product Otoacoustic Emissions: Right Ear dB Response (MEAN) Minus Left Ear dB Response (MEAN)

kHz	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
2 kHz	5	3	1	2	1	0	1
4 kHz	6*	6*	4	2	4	3	6*
6 kHz	5	1	-1	-2	1	2	1
8 kHz	4	1	-1	1	0	3	-1
10 kHz	3	6*	2	-1	0	2	-3
12 kHz	0	-1	1	-3	-2	-8*	-5

Note: *Asymmetry (Difference of ≥6 dB)

Furthermore, audiological history was taken at the baseline, and already, eight participants reported difficulty localising (n = 4 from HJH, n = 4 from SRH). This was before the DR-TB treatment was started and before asymmetry was noted.

Yet, half of the participants displayed some sort of mild hearing loss at baseline, ranging from 30 dB in a single frequency to 40 dB in four frequencies bilaterally.

6.1.5. Percentage and Overall Changes in Hearing/Cochlear Function

The overall changes in hearing and cochlear function from baseline at the various frequencies are outlined in Table 6.7; DPOAEs are shown from 2 kHz to 12 kHz, while PTA is shown from 3 kHz to 16 kHz. Each participant has two results under each of these frequencies. The top result is of the right ear, while the bottom is the left ear. These PTA results are then related to the various grading scales and their applicability. As there is no grading scale for DPOAEs, any loss of 6 dB or greater was considered a loss and marked as 'yes'.

In some instances, with PTA, loss of hearing is observed in the ultra-high frequencies, yet not depicted as a gradable loss on a grading scale. For example, participant 2 showed a change of 10 dB in three frequencies in the right ear and 10 dB in the left ear, however, they are not consecutive frequencies.

Although the sample size was small, and the percentage is not entirely suitable for such a small sample, it depicts how different the results can be, based on the different grading scales used. The number of participants that experienced hearing loss thus further described as a percentage. Fifteen participants completed more than the baseline measurements, and so these were used to calculate the percentage.

When looking at the DPOAEs, all participants had readings showing a significant change of at least 6 dB in at least one frequency in at least one ear. This could be regarded as

100% of the participants had loss of cochlear function. Different percentages can be described with PTA, depending on which frequencies and grading scales used.

When using at the TUNE grading scale, 14 of the 15 could be graded with a hearing loss; whenever they completed the study, whether at T1 or T6. This shows that 93% experienced some sort of loss of hearing. The CTCAE only graded up to 8 kHz, and thus only identified one hearing loss (7%). The ASHA method to describe hearing loss identified 14 of the 15 participants with significant hearing loss (93%). The ASHA scale did not specify the specific frequencies that it includes, and so it was used for all the frequencies up to and including 16 kHz.

Thus, depending on which frequency range is used to describe hearing loss, between 7% to 93% of participants experienced ototoxicity. However, 7% experienced this at 8 kHz or below. Although the sample is small, it still indicates the different results based on the different grading scales used.

Table 6.7

Overall Change in Hearing from Baseline with Ototoxicity Grading Scales (right and left ears)

Grading Scales							DPOAE Level (dB)						PTA (dB) (Overall change from baseline to week of dropout)									
Participant	**Weeks in the Study (T)**	**EAR**	**DPOAE 6 dB**	**TUNE**	**CTCAE**	**ASHA**	**2 kHz**	**4 kHz**	**6 kHz**	**8 kHz**	**10 kHz**	**12 kHz**	**3 kHz**	**4 kHz**	**6 kHz**	**8 kHz**	**9 kHz**	**10 kHz**	**11.2 kHz**	**12.2 kHz**	**14 kHz**	**16 kHz**
1	0,1,2	R	YES	2a	-	YES	-19.5	-3	-7	-20	-9	-9	-5	5	0	-10	0	-5	-30	-50	-45	-5
		L	YES	1a	-	YES	-7	-8	-8.5	-1	-13	-6	0	-5	0	-5	0	-5	-5	-10	-15	-60
2	0,1	R	-	0	-	NO	*	*	*	*	*	*	0	0	-15	0	-5	0	-10	-5	-5	-15
		L	-	1a	-	NO	*	*	*	*	*	*	0	0	5	-10	-5	0	0	-5	-5	-10
4	0,1,2,3,4 ,5,6	R	YES	1a	-	YES	-9.5	-12	-8.5	-13	-10.5	-15	0	-10	-10	-5	-5	-5	0	-10	-10	-10
		L	YES	0	-	NO	-6	-5.5	-8	-10	-5.5	-7.5	-5	-5	-10	-5	0	0	-5	-5	-10	-5
5	0,1,2,3,4 ,5,6	R	YES	1a	-	YES	-13	-12	-21.5	-10	0	0	5	-5	-15	-5	-10	-5	-10	-5	-10	-5
		L	YES	2a	-	YES	-11.5	-13	-16	-13.5	-22	-20	-10	-10	-5	-10	-25	-25	-35	-35	-45	-35
6	0,1,2	R	YES	0	-	YES	-7.5	-1	-6	8	-6	-7.5	0	-5	0	-5	0	5	-5	-10	-35	0
		L	YES	0	-	YES	-1	-7.5	1.5	-2.5	-5.5	-1	-5	-5	5	0	0	0	0	-5	0	-30
7	0,1,2,3,4 ,5,6	R	YES	2a	-	YES	-8	-13	-1.5	-20	-17	-29	0	-5	-5	-10	-10	-15	-50	-50	-60	-50
		L	YES	0	-	YES	-16	-7.5	-6.5	-7.5	-11	0	0	-5	0	-5	-15	-5	-5	0	-5	-25

Grading Scales							DPOAE Level (dB)						PTA (dB) (Overall change from baseline to week of dropout)									
Participant	Weeks in the Study (T)	EAR	DPOAE 6 dB	TUNE	CTCAE	ASHA	2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.2 kHz	14 kHz	16 kHz
8	0,1,2,3,4	R	YES	2a	-	YES	-4	-4	-16.5	-18	-14.5	-15	0	0	-10	0	-10	-10	-50	-40	-30	-10
	,5,6	L	YES	1a	-	YES	-12.5	-6	-13	-5.5	-7	-17.5	-5	0	-10	0	-10	-5	-10	-10	-15	-10
9	0,1,2,3,4	R	YES	1a	-	YES	-29	-6.5	-16	-16	-16	-4.5	-10	0	-10	-5	0	-5	-15	-10	-30	-15
	,5,6	L	YES	1a	-	YES	-7	-8	-10	-8	-14	-17	0	0	-5	-5	-5	-10	-15	-15	-15	-25
10	0,1,2,3,4	R	YES	2a	-	YES	-10.5	-18	-6	-18	-20	-15	0	-5	0	-35	-50	-45	-50	-35	0	-5
	,5,6	L	YES	2a	-	YES	-7	-1	-4	-2	-12	0	15	10	5	-15	-35	-50	-20	0	0	0
12	0,1	R	YES	2a	1	YES	-11	-6	-23	-8	-36	-34.5	-5	-5	-15	-15	-45	-55	-70	-65	-60	-50
		L	NO	1a	-	YES	-1	0	1.5	2.5	-4	-3.5	15	10	10	0	10	0	-15	-15	-20	0
14	0,1,2,4	R	YES	1a	-	YES	-11.5	-8.5	-1.5	-1.5	-18	-6	-5	0	0	-5	-5	-10	-5	-15	-10	-10
		L	YES	1a	-	YES	-11.5	-10.5	-17.5	-10	-17	-22	0	0	-10	-10	0	-5	-5	-10	-35	-30
15	0,1,	R	YES	1a	-	YES	-6	0.5	-14	-11	-6	0	0	0	-10	-10	5	5	-10	-10	0	-5
		L	YES	1a	-	YES	-0.5	-5	-5.5	-5.5	-20	-1.5	0	-15	-10	-10	0	-15	-10	-10	-15	0
16	0,1,2,3,4	R	YES	2a	-	YES	-10	-4	-9	-5.5	-5.5	-4	-10	5	0	0	0	0	-10	-20	-5	-5
		L	YES	1a	-	YES	-7	-4.5	0	0	-9.5	-0.5	-5	-10	-5	-10	0	0	-5	0	-20	-5
17	0,1,2,3,4	R	YES	2a	-	YES	-11	-20.5	-32	-21.5	-27.5	-6.5	-20	-10	-45	-25	-20	-20	-15	-20	-10	0

Grading Scales								DPOAE Level (dB)						PTA (dB) (Overall change from baseline to week of dropout)									
Participant	**Weeks in the Study (T)**		**EAR**	**DPOAE 6 dB**	**TUNE**	**CTCAE**	**ASHA**	**2 kHz**	**4 kHz**	**6 kHz**	**8 kHz**	**10 kHz**	**12 kHz**	**3 kHz**	**4 kHz**	**6 kHz**	**8 kHz**	**9 kHz**	**10 kHz**	**11.2 kHz**	**12.2 kHz**	**14 kHz**	**16 kHz**
			L	YES	1a	-	YES	-23.5	-23.5	-27	-3.5	-20.5	0.0	5	-25	-45	-5	0	-20	-20	-10	10	-5
18	0,1,3,4,5		R	YES	1a	-	YES	-15	-24	*	*	*	-16	0	-5	0	0	-10	-10	-15	-10	-20	-20
			L	YES	2a	-	YES	-3	-9	-3	-8	0	-1	0	-5	-5	-10	-15	-25	-15	-25	-10	0

Note: '**–**' indicates no grade is applicable, * Missing data due to poor signal to noise ratio, TUNE Grading system only grades up to 12.5 kHz and does not include 9 and 11.2kHz. CTCAE only grades up to 8 kHz. ASHA is for all the frequencies, Audiology results not included for those that dropped out before week 2, Audiology results included are at last study visit before dropout or last audiology results available. Yellow shading indicates the limits of the audiometer.

6.1.6. Weeks of Greatest Change in Hearing/Cochlear Function

The time period/ study week that displayed the greatest change with PTA and DPOAEs was examined in further detail. Although this was not a direct sub-aim, it is important to establish to assist in the development of an ototoxicity monitoring protocol.

Table 6.8 shows the specific weeks where the greatest mean change in PTA (high and ultra-high frequencies) and DPOAEs occurred. The means were calculated with the ears combined. The most significant changes with DPOAEs from the previous study visit was noted at week 2 at 2 kHz, 8 kHz, 10 kHz, and 12 kHz. The greatest changes with PTA from the previous study visit was noted at both weeks 2 (11.2 kHz, 12 kHz and 14 kHz) and 6 (6 kHz, 8 kHz, and 10 kHz).

Table 6.8

Study Weeks of Biggest Mean Change in dB at various frequencies from the previous study visit

	OAE (dB)						**PTA (dB)**									
	2 kHz	**4 kHz**	**6 kHz**	**8 kHz**	**10 kHz**	**12 kHz**	**3 kHz**	**4 kHz**	**6 kHz**	**8 kHz**	**9 kHz**	**10 kHz**	**11.2 kHz**	**12.5 kHz**	**14 kHz**	**16 kHz**
Week 2	-4.08	-3.65	-4.35	-5.15	-6.31	-3.98	1	-1.67	-3.00	-3.17	-3.39	-3.67	-10.17	-7.83	-8	-5.17
Week 4	-2.64	0.00	0.02	-0.65	-2.44	-1.20	-2.11	1.94	3.56	3.17	-1.33	-1.33	0.72	-2.44	-3.11	-4.00
Week 6	-0.64	-1.52	-1.45	-1.81	0.11	-1.35	-1.11	-2.50	-6.11	-3.53	-2.78	-3.89	-1.94	-0.56	0.00	-0.28
Week 8	-1.35	-4.06	-3.17	-1.06	-2.39	-0.45	0.28	-2.50	-2.78	-1.19	-0.83	-1.94	-2.50	-1.11	-2.78	-1.39
Week 10	1.07	2.12	3.18	-1.29	2.14	-1.81	0.52	2.58	4.05	-2.78	-5.24	-3.10	-2.18	-4.13	-1.47	0.12
Week 12	-3.52	-1.77	-4.86	-1.83	-3.57	-2.92	0.60	-0.77	-1.96	-0.83	-1.01	-1.07	-6.01	-1.85	-3.81	-5.54
Week of biggest change from previous study visit	2	8	12	2	2	2	4	10	6	6	10	6	2	2	2	12

6.1.7. Differences in hearing for participants on treatment with kanamycin and capreomycin

At SRH, capreomycin was used when those taking kanamycin started to show a decline in hearing. They were subsequently switched onto capreomycin to reduce the ototoxicity. These differences in change in hearing and cochlear function were therefore examined at weeks 10 and 12 using the PTA and DPOAEs.

Table 6.10 depicts the change in cochlear function (DPOAEs) and change in hearing (PTA) from baseline for weeks 10 and 12. Week 10 was included as there was only one participant on capreomycin at week 12. The frequencies with an asterisk show where kanamycin resulted in more ototoxicity than capreomycin. Hence without an asterisk is where capreomycin resulted in more ototoxicity.

It is difficult to ascertain whether kanamycin or capreomycin is more ototoxic according to this study. Often, the participants that were experiencing ototoxicity were switched to capreomycin. Therefore, it is possible that these patients were more susceptible to ototoxicity and cannot to be attributed to the toxicity of the drug, but possibly to other factors.

However, the differences at week 10 and 12 were calculated. It is important to note that the capreomycin column includes participants that were not necessarily on capreomycin throughout the study, as they all started on kanamycin. Hence, weeks 10 and 12 were used to allow a better determination of hearing loss from capreomycin. The values in Table 6.9 are means values of the participants and ears combined at the relevant frequency and specific week 10 or week 12.

Table 6.9

Differences in hearing loss between kanamycin and capreomycin at weeks 10 and 12: Change in dB in right and left ears combined from baseline

Measure	Frequency (kHz)	Week 12				Week 10			
		Capreomycin (*n* = 1)		Kanamycin (*n* = 5)		Capreomycin (*n* = 2)		Kanamycin (*n* = 5)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
DPOAE (dB)	2*	-8.8	2.5	-11.2	7.1	-6.5	6.2	-8.1	4.5
	4	-9.5	12	-8.9	3.4	-11.4	10.1	-5.4	4.2
	6*	-5	1.4	-10.6	5.9	-3.5	1.3	-6.5	8.9
	8*	-10	11.3	-11.8	4.8	-9.3	8.1	-10.2	5
	10	-16	5.7	-12.5	6.4	-10.7	10.1	-8.4	6.2
	12*	-7.5	10.6	-11.7	9.4	-8	8.7	-9.1	10.6
PTA (dB)	3*	7.5	10.6	-0.8	4.9	0	0	-2	2.6
	4*	2.5	10.6	-2.9	3.9	0	7.1	-3	2.6
	6*	2.5	3.5	-6.3	4.2	-1.3	2.5	-5.5	9.3
	8	-25	14.1	-8.3	3.3	-15	14.7	-4.5	6.4
	9	-42.5	10.6	-14.6	7.4	-27.5	18.5	-8	10.6
	10	-47.5	3.5	-15	7.1	-32.5	18.5	-6.5	12
	11.2	-35	21.2	-22.1	18.6	-25	16.8	-12.5	18.4
	12.5*	-17.5	24.7	-17.9	17.2	-17.5	15.5	-15.5	19.4
	14*	0	0	-19.2	18	-6.3	11.1	-19	19.1
	16*	-2.5	3.5	-16.3	14.7	-5	10	-13	17.5

*frequency where kanamycin ototoxicity in greater

6.1.8. Summary of Audiological Results

In summary, this section addressed the audiological aim which was to determine the changes in hearing levels in patients receiving treatment with kanamycin and capreomycin for DR-TB. This included investigating the prevalence of abnormal findings on baseline hearing assessments and determine the change in hearing levels from baseline.

The changes were noted using PTA and DPOAEs. With the PTA, no clinically significant mean change was noted in the low frequencies bilaterally, yet significant change occurred from T0 to T6 in specific high frequencies; 6 kHz and 8 kHz in right ears and 8 kHz in left ears. Furthermore, the ultra-high frequencies showed significant hearing loss bilaterally, as expected, except for 12.5 kHz, 14 kHz and 16 kHz in the left ears.

Significant changes with DPOAEs were also observed from T0 to T6 bilaterally in all frequencies except 12 kHz in the left ear.

Percentage of ototoxicity was calculated, even though not ideal for a small sample. These percentages were difficult to ascertain due to various grading systems available to classify hearing loss. Despite the small sample size, the percentage was calculated from the 15 participants that completed more than the baseline visit. DPOAEs showed a mean loss of 6 dB or more at more than one frequency, and so 100% could be described as having a loss of cochlear function. Different percentages can be described with PTA, depending on which frequencies and grading scales used. When using the TUNE scale and ASHA system, 93% could be described as having ototoxicity, or ototoxicity in 7% of the sample when using the CTCAE scale. This variability is a result of the different scales, and thus a standardised scale is necessary for this population, in order to obtain reliable and standardised percentages.

The asymmetry differs on PTA and DPOAEs. Differences of 10 dB between ears for PTA and 6 dB for DPOAESs were considered as asymmetry. Asymmetry was noticed on visits T1, T4 and T6 with PTA, yet on visits T0, T1, T5 and T6 with DPOAEs.

In this current study, kanamycin revealed more ototoxicity than the capreomycin as determined by PTA and DPOAEs, as would be expected. Also, although not a sub-aim, yet useful for recommendations for a monitoring protocol, week 2 was found to show the greatest change in the DPOAEs and weeks 2 and 6 showed the greatest change with the PTA.

6.2. Pharmacokinetic Findings of Kanamycin and Capreomycin

In this section, the findings of the following sub-aims and objectives are addressed:

To investigate the kanamycin and capreomycin pharmacokinetics in patients undergoing treatment for DR-TB.

- To investigate the peak and trough levels of kanamycin and capreomycin at two weekly intervals for the first three months of treatment.
- To investigate the relationship between the kanamycin and capreomycin kinetics with creatinine levels.
- To examine the relationship between the pharmacokinetics/ pharmacodynamics of kanamycin and capreomycin to culture conversion after the three-month period.

6.2.1. Investigation of the Mean Peak and Trough Levels for kanamycin and capreomycin: Pharmacokinetic Results

Pharmacokinetic factors were calculated for kanamycin and capreomycin. These factors included doses (mg/kg), peaks (μg/ml), troughs (μg/ml), half-lives (hours), and volumes of distribution (ℓ/kg).

Tables 6.10 and 6.11 depicts the pharmacokinetic results from baseline (T0) up until week 12 (T6) (2 weekly intervals) as well as the mean pharmacokinetic results from T1 to T6 respectively. The results are described separately for kanamycin and capreomycin, where the

mean dose/kg, peak levels, trough levels, half-lives and volume of distribution are described in both tables.

The weight of participants on kanamycin remained relatively stable from T0 to T6 within the weights 51.2kg to 55.4kg (mean: 54,13kg, SD±1.55). The average weights of participants on capreomycin fluctuated between 48.8kg and 56.3kg (mean: 52.82kg, SD ±3.8) (Table 6.10).

The average dosages of kanamycin varied between the weeks from 13.5 mg/kg - 16 mg/kg (mean: 14.56; SD 1 and 4.8). The average peak levels of kanamycin ranged between 4.4 µg/ml – 41.2 µg/ml (mean: 20.03; SD ±2.3 and 15.4) throughout the weeks with the trough levels of kanamycin ranging between 0.4 µg/ml – 2.4 µg/ml (mean: 1.33; SD ±0.3 and 4.6).

The average half-life of kanamycin varied between 5 – 13.7 hours (mean: 9.3; SD ±0.6 and 6) throughout the weeks and the average volume of distribution of kanamycin varied between 0.4 ℓ/kg – 5.8 ℓ/kg (mean: 2.47; SD ±0.2 and 5,1) throughout the weeks (Table 6.11). Overall, the pharmacokinetic results appeared erratic.

The average dosages of capreomycin varied between the weeks from 13.5 mg/kg – 17.8 mg/kg (mean: 15.45; SD ±3.2 and 0) respectively. The average peak levels of capreomycin ranged between 3.3 µg/ml – 16.8 µg/ml (mean: 8,1; SD 1.8 and 16.8) throughout the weeks with the trough levels of capreomycin ranging between 0.5 µg/ml – 1.9 µg/ml (mean: 0.73; SD± 0 and 4).

The average half-life of capreomycin varied between and 6.2 – 9.6 hours (mean: 7.2; SD ±0.8 and 1.5) throughout the weeks and the average volume of distribution of capreomycin varied between 1.3 ℓ/kg – 6.9 ℓ/kg (mean: 3.3; SD ±1,1 and 5.4) throughout the weeks (Table 6.11). Overall, the pharmacokinetic results appeared erratic.

The total drug levels have also been averaged out between from T0 and T6 and can be seen in Table 6.12. The overall peak levels differed between kanamycin and capreomycin, with peak levels of 20 μg/ml and 8.1 μg/ml respectively.

Table 6.10

Pharmacokinetic Results for kanamycin and capreomycin from T0 to T6

		T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 (KM)	T2 (CM)	T3 (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
n		22	0	11	4	8	3	5	4	5	5	5	2	5	1
dropout /CM*		0	0	7	0	3	1	3	0	0	0	0	3	0	1
Gender	M	7	0	3	0	2	0	1	1	1	1	1	0	1	0
	F	15	0	7	4	6	3	4	3	4	4	4	2	4	1
Age	Mean	33.8		31.8	32.1	28.3	32.0	26.5	38.0	27.8	35.0	26.6	36.7	26.6	35.4
(in years)	SD	7.3		8.3	7.8	6.8	8.3	6.1	2.2	6.2	7.2	6.1	2.0	6.1	
	Min	18.6		18.6	18.6	18.7	22.5	18.7	35.2	18.7	22.6	18.8	35.3	18.8	35.4
	Max	42.8		42.0	42.0	40.5	38.2	-32.6	40.5	32.6	40.6	32.7	38.1	32.7	35.4
	Med	35.1		30.1	32.5	29.4	35.2	29.6	38.2	30.0	38.1	29.7	36.7	29.7	35.4
Weight	Mean	54.1		53.5	53.8	55.4	48.8	51.2	48.9	54.0	50.5	55.4	56.3	53.8	55.6
(in kg)	SD	10.9		8.7	9.9	2.7	6.8	6.8	8.0	1.4	8.5	3.6	⁂	7.7	⁂
	Min	34.0		37.0	52.8	54.0	41.9	40.0	43.7	52.0	41.9	50.2	56.3	40.0	55.6
	Max	73.0		69.0	72.4	59.4	58	-57.0	58.1	55.0	59.4	59.0	56.3	59.0	55.6
	Med	54.5		54.0	54.0	54.0	46.4	54.0	44.8	54.5	50.4	57.0	56.3	57.0	55.6
Dose	Mean	16.0		14.1	14.3	13.7	15.3	14.9	13.5	14.8	13.9	13.5	17.8	14.9	18.0
(mg/kg)	SD	4.8		1.5	1.8	2.1	3.9	2.3	3.2	2.0	3.5	1.0	⁂	2.5	⁂
	Min	11.6		12.0	14.2	10.6	10.8	13.2	11.2	13.6	11.2	12.7	17.8	12.7	18.0
	Max	34.1		18.0	18.0	17.8	17.9	-18.8	18.8	18.3	17.9	14.9	17.8	18.8	18.0
	Med	14.5		13.9	13.9	13.9	17.2	13.9	12.2	13.9	12.6	13.1	17.8	13.2	18.0
Peak	Mean	21.0		18.2	16.8	11.1	6.4	10.2	5.9	34.1	3.3	41.2	⁂	4.4	⁂
(µg/ml)	SD	38.6		17.4	16.8	7.9	2.1	3.1	1.3	31.1	1.8	15.4	⁂	2.3	⁂

		T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 (KM)	T2 (CM)	T3 (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
	Min	1.1		4.6	55.2	3.7	4.9	6.9	4.9	12.1	2.1	30.4	⁑	2.0	⁑
	Max	148.9		55.2	55.2	26.2	7.9	-13.1	13.1	56.1	4.6	52.1	⁑	7.5	⁑
	Med	5.2		12.4	8.0	7.7	6.4	10.6	5.9	34.1	3.3	41.2	⁑	4.1	⁑
Trough	Mean	0.4		2.4	1.9	1.4	0.5	1.6	0.5	1.7	0.5	0.9	0.5	0.9	0.5
(µg/ml)	SD	0.3		4.6	4.0	1.5	0.0	1.9	0.1	1.9	0.1	0.6	0	0.4	0
	Min	0.1		0.5	15.7	0.1	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.5
	Max	1.0		15.7	15.7	5.0	0.5	-4.9	4.9	5.0	0.7	1.6	0.5	1.6	0.5
	Med	0.5		0.9	0.5	1.0	0.5	0.9	0.5	0.9	0.5	0.5	0.5	1.0	0.5
Half-life	Mean	7.5		7.2	6.7	7.2	6.3	13.3	6.2	11.2	9.6	5.0	⁑	13.7	⁑
(hours)	SD	5.5		2.5	2.5	1.5	0.8	10.3	0.8	9.5	1.5	0.6	⁑	6.0	⁑
	Min	2.2		4.5	13.0	5.9	5.7	6.0	5.7	4.4	8.5	4.5	⁑	10.5	⁑
	Max	19.4		13.0	13.0	9.2	6.9	-20.6	20.6	17.9	10.7	5.4	⁑	22.7	⁑
	Med	5.3		6.6	6.2	6.3	6.3	13.3	6.2	11.2	9.6	5.0	⁑	10.8	⁑
V_D (ℓ/kg)	Mean	4.5		1.3	1.3	2.3	2.2	2.2	2.7	0.8	6.9	0.4	⁑	5.8	⁑
	SD	5.1		1.1	1.1	1.5	0.1	1.0	1.3	0.9	5.4	0.2	⁑	5.1	⁑
	Min	0.1		0.3	0.3	0.6	2.2	1.1	1.8	0.2	3.1	0.2	⁑	2.1	⁑
	Max	19.7		3.3	3.3	4.8	2.3	-3.0	3.6	1.8	10.7	0.5	⁑	13.3	⁑
	Med	2.8		0.8	0.8	2.7	2.2	2.5	2.7	0.4	6.9	0.4	⁑	4.0	⁑

Note: *number of participants who dropped out from the study or who were switched to capreomycin, ⁑missing pharmacokinetic data due to haemolysis, Med=median value

Table 6.11

Total Mean and SD Pharmacokinetic Results of kanamycin and capreomycin from T1- T6

	Kanamycin		**Capreomycin**	
	Mean	**SD**	**Mean**	**SD**
Dose (mg/kg)	14.6	2.3	15.5	2.7
Peak (μg/ml)	20.0	16.5	8.1	5.5
Trough (μg/ml)	1.3	1.6	0.7	1.0
Half Life (hours)	9.3	5.1	7.2	1.4
Volume of Distribution (ℓ/kg)	2.5	2.1	3.3	2.0

The total number of participants on kanamycin and on capreomycin is not mentioned in table 6.12. This is due to the fact that all participants started on kanamycin, and then some were switched to capreomycin, yet at different weeks. Only five participants that were initiated on kanamycin at T0 remained on kanamycin at T6. The overall kanamycin and capreomycin pharmacokinetic values were therefore calculated throughout the weeks where they used.

6.2.2. The relationship between the kanamycin and capreomycin pharmacokinetics with creatinine levels

The creatinine levels (adjusted to gender) are described in relation to the kanamycin and capreomycin trough levels (Table 6.12).

Reduced Calculation of the Creatinine Clearance (CrCl) is measured below 80ml/min (Messa et al., 1988) and trough levels exceeding 10 μg/ml are considered possibly toxic (Black et al., 1976).

For participants taking kanamycin, the average creatinine clearance was reduced, yet the drug was still cleared through the system, as seen with trough levels below 10 μg/ml (Table 6.12).

For participants taking capreomycin, the majority of the creatinine clearance was within the normal range (80 – 130 ml/min). The trough levels were below 10 µg/ml showing appropriate clearance, even when the creatinine levels were reduced as in weeks two and four (Table 6.12).

Table 6.12

CrCl (adjusted according to gender) in relation to mean trough levels

	Kanamycin		**Capreomycin**	
	CrCl Mean (ml/min)	**Trough Mean (µg/ml)**	**CrCl Mean (ml/min)**	**Trough Mean (µg/ml)**
T0	60.88	0.48	*	*
T1	68.92	2.45	66.1	0.45
T2	81.56	1.44	77.37	0.48
T3	59.86	1.57	97.09	0.46
T4	59.28	1.69	163.97	0.55
T5	57.11	0.92	88.12	0.5
T6	58.28	0.99	‡	0.5

Note: *participants were not taking capreomycin at baseline hence N/A at baseline, ‡ At week 12, the creatinine results could not be found on the NHLS database, hence unavailable.

6.2.3. The Relationship between the Pharmacokinetics/ Pharmacodynamics of kanamycin and capreomycin to Culture Conversion

The objective was to establish whether participants had culture converted by the end of the week 12, or the last week before dropout, in order to document differences between kanamycin and capreomycin. 6.14 described the culture results for kanamycin and capreomycin. However, in some instances, that are explained, culture results could not be accessed (Table 6.13).

It is evident, that in two instances participants converted slightly later than at HJH. Those participants at SRH were on capreomycin. Despite the low peak levels, participants appeared to have culture converted (Table 6.13).

Table 6.13

Culture conversion results from participants of kanamycin (n = 9) and capreomycin (n = 13)

	Helen Joseph Hospital (kanamycin)	**South Rand Hospital (mostly capreomycin)**
n	9	13
Missing culture results	3	4
Reasons for missing culture results	One participant dropped out due to transfer Sizwe Hospital One participant withdrew from the study prior to transfer to another hospital. -One participant refused hospital treatment, and so no further culture results were available	Three participants were transferred to Sizwe Hospital* Two participants passed away before culture results were available
Existing culture results	Six participants converted by month one	Seven participants converted by month one. One participant converted by week six One participant converted by month two

Note: *Culture results from participants who were transferred to Sizwe Hospital could not be accessed.

6.2.4. Summary of kanamycin and capreomycin Pharmacokinetics

In summary, the pharmacokinetics yielded erratic results. The total dosages of kanamycin and capreomycin were similar, although did differ slightly. The average dosages

varied between the weeks from 13.5 mg/kg - 16 mg/kg (mean: 14.56; ± 1 - 4.8) and 13.5 mg/kg – 17.8 mg/kg (mean: 15.5; ±3.2 and 0) respectively for kanamycin and capreomycin.

The most erratic results were within the peak levels, particularly with kanamycin. The average peak levels of kanamycin and capreomycin ranged between 4.4 μg/ml – 41.2 μg/ml (mean: 20.03; SD ±2.3 and 15.4) and 3.3 μg/ml – 16.8 μg/ml (mean: 8.1; SD 1.8 and 16.8) throughout the weeks, yet the trough levels were always below 10 μg/ml and not within a toxic range.

Average CrCl was reduced for those taking kanamycin, yet majority was within the normal range for capreomycin.

All participants that could be documented culture converted within the first two months. However, this included one negative culture, in comparison to the two standard two consecutive cultures. This was not possible to document due to the short duration of the study.

6.3. Pharmacokinetics of kanamycin and capreomycin in Relation to Hearing Levels

This section discusses the following sub-aims:

Examine the relationship between kanamycin and capreomycin pharmacokinetics and hearing levels

- To examine the relationship between kanamycin and capreomycin dosing and hearing levels.
- To explore the relationship between kanamycin and capreomycin dosing and the progression of hearing loss.

6.3.1. The Relationship between Pharmacokinetics of kanamycin and capreomycin, including Dosing, with Hearing Levels

The pharmacokinetic results are presented separately for each week (T0 to T6) in relation to the change in hearing at the various frequencies for both kanamycin and capreomycin separately. The dose per kilogram, peak and trough levels, as well as half-lives and volumes of distribution, are mentioned. The peak readings were measured at 4 to 6 hours after the injection was administered while the trough measurements were taken 30 minutes prior to the administration of the injection (after the previous days' injectable).

The audiology results are tabulated for both DPOAEs and PTA, which are figures depicting the change from baseline in decibels. For these DPOAE and PTA results, the change was calculated by dB level at baseline minus dB reading at the various weeks; a negative result shows the deterioration of hearing at the specific week, whereby a positive result shows an improvement from baseline at that specific frequency.

The dB responses for DPOAEs and PTAs are tabulated for each frequency for each ear. The right ear response is noted on the first line in the relevant section, with the left ears response being noted under the right ear. A significant change was considered as 6 dB for DPOAEs and 10 dB for PTA.

The high frequencies and UHF are included in this section. However, as 3 kHz was not tested with the DPOAEs, 2 kHz and above are included, while 3 kHz and above are included for PTA.

Pharmacokinetically the distribution of the drugs should be equal to both ears. Drugs distribute as a percentage of body weight (Burton, Shaw, Schentag & Evans, 2006), which does not allow the drugs to enter the endolymph differently in the right and left ears. Therefore, the *mean levels* are described as the combination of the right and left ears at each frequency.

In a few instances, there is missing pharmacokinetic, DPOAE and PTA data. This missing data is highlighted in purple. The missing pharmacokinetic data is generally a result of haemolysis of the samples or errors with small samples drawn from the patients. In the cases of missing DPOAE data, issues with SNR ratios, repeat reading and equipment errors occurred, where the missing PTA data was a result of uncooperative or unresponsive participants. In one instant, 9 kHz was not tested due to tester error.

Lastly, the responses highlighted in yellow show the limit of the machine. The hearing loss possibly deteriorated more than noted, yet could not be recorded by the relevant equipment. Therefore, for statistical purposes, the maximum limit response was recorded, even when the response may have been worse.

6.3.1.1. Baseline – study visit T0.

The baseline measurements did not measure the change in hearing, and so hearing levels are not mentioned in this table (Table 6.14). Table 6.1 describes the pharmacokinetics results of kanamycin; capreomycin was not used at baseline. The details the peak readings that were measured at the first dose of the injectable (four to six hours post the first injection), while the trough measurements were taken the following day, 30 minutes prior to the second injection.

All participants were given kanamycin at the baseline, even in cases where they presented with hearing loss. The average dose per kilogram was 16 mg/kg (±4.8) (Table 6.14).

Peak levels were calculated at baseline, with the mean being 21 μg/ml (SD ± 38.6). The minimum peak was 1.1 μg/ml, and the maximum was 148.9 μg/ml. The trough levels included a mean of 0.4 μg/ml (SD ± 0.3). The minimum trough level was 0.1 μg/ml while the maximum was 0.9 μg/ml (Table 6.14).

The half-lives were also calculated when possible for each participant and measured in hours. The mean half-life was 7.5 hours (SD ± 5.5) with a mean volume of distribution being 4.5 ℓ/kg (SD ± 5.1 ℓ/kg) (Table 6.14).

Table 6.14

Baseline pharmacokinetic results of kanamycin (n = 22)

Study ID	Age (years)	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (I /kg)
1	24.4	F	48	15.6	5.2	0.1	3.9	2.8
2	40.1	M	58.7	12.8	*	0.5	*	*
3	40.7	M	59	12.7	2.5	0.1	4.6	4.9
4	21.2	F	42	18.0	7.9	0.1	3.4	2.1
5	32.4	M	52.3	14.4	2.6	0.1	4.7	5.4
6	29.1	F	55	13.6	6.6	0.9	8.1	2.3
7	18.6	F	54	13.9	2.3	1.0	19.3	10.0
8	29.4	F	50	15.0	3.3	1.0	12.9	6.1
9	30.1	F	53	14.2	35.3	0.9	4.6	0.4
10	35.1	F	63	15.9	*	0.5	*	*
11	35.11	F	58	12.9	1.1	0.5	19.4	19.7
12	41.11	F	69	14.5	26.9	0.1	7.1	0.5
13	42.8	M	35	21.4	9.3	0.5	5.3	2.3
14	22.4	F	42	34.1	*	0.5	*	*

Study ID	Age (years)	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (I /kg)
15	41	F	34	14.7	*	0.5	*	*
16	40.4	M	64.5	11.6	*	0.5	*	*
17	38.1	F	41.9	17.9	4.9	0.5	6.8	3.8
18	37.11	F	71	14.1	*	0.5	*	*
19	33.5	F	48.4	20.7	3.3	0.5	8.2	6.9
20	40.3	F	73	13.7	*	0.5	*	*
21	29.4	M	64	11.7	148.9	0.1	2.2	0.1
22	40.9	M	55	18.3	55.2	0.1	2.6	0.3
Mean	33.8	F	54.13	16.0	21.0	0.4	7.5	4.5
STD	7.3		10.94	4.8	38.6	0.3	5.5	5.1
Min	18.6		34	11.6	1.1	0.1	2.2	0.1
Max	42.8		73	34.1	148.9	1.0	19.4	19.7
Med	35.1		54.5	14.5	5.2	0.5	5.3	2.8

* indicating missing data due to haemolysis

6.3.1.2. Week 2 – study visit T1.

The participant's pharmacokinetic readings and their change in hearing from baseline at week two are described in Table 6.15 (kanamycin participants) and 6.16 (capreomycin participants).

Four of these 15 participants had switched to capreomycin by week two due to adverse events. Therefore, kanamycin and capreomycin results are presented separately in the tables below (see Table 6.15 and 6.16).

The mean dose of kanamycin and capreomycin was similar, at 14.13 mg/kg (SD ± 1.5) and 14.3 mg/kg (SD ± 1.8) respectively. Peak levels for kanamycin and capreomycin were 18.2 μg/mg (SD ± 17.4) and 16.8 μg/mg (SD ±16.8) respectively with trough levels of 2.4 μg/mg (SD ±4.6) and 1.9 μg/mg (SD ±4) respectively. The half-life was 7.2 hours (SD ±2.5) for kanamycin and 6.7 hours (SD ±2.5) for capreomycin. The volume of distribution was equal between kanamycin and capreomycin of 1.3ℓ/ kg hours (SD±1.1).

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 8 kHz and 10 kHz of -7.1 dB (SD ±6.8) and -8.2 dB (SD ±9.4) respectively. There were significant individual changes at all the other frequencies, yet not a mean significant change. There was no mean significant change (10 dB) noted in the PTA. However, there were significant individual changes noted at each PTA frequency (see Table 6.15).

For those participants that had been switched to capreomycin, a mean significant change of DPOAEs was noted at 10 kHz of -6.3 dB (SD ±8.8) and of -10.2 dB at 11.2 kHz with PTA. Individual significant changes were noted at all frequencies with DPOAEs and PTAs, yet this was not mean results (Table 6.16)

It is possible that a mean significant change was observed in the DPOAEs highlighted in yellow. The limits of the machined cannot describe responses effectively as once the DPOAEs were absent, they could not be '*more absent'*.

Table 6.15

Week 2 Pharmacokinetic Results and Change in Audiology Results from Baseline for kanamycin (Audiology Baseline minus Week 2: Right and Left ears, n = 11)

ID	Age (yrs.)	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
1	24.5	F	52.8	14.2	55.2	15.7	13.0	0.3	R	-9.5	-6.0	-6.0	-21.0	-6.0	10.0	0.0	0.0	-5.0	-15.0	-5.0	0.0	0.0	-5.0	-20.0	-5.0
									L	10.0	3.0	1.5	-2.5	-13.0	-6.0	10.0	5.0	15.0	0.0	-15.0	0.0	0.0	0.0	0.0	5.0
2	40.1	M	58.7	12.8	30.7	4.7	8.9	0.5	R	*	*	*	*	*	*	0.0	0.0	-15.0	0.0	-5.0	0.0	-10.0	-5.0	-5.0	-15.0
									L	*	*	*	*	*	*	0.0	0.0	5.0	-10.0	-5.0	0.0	0.0	-5.0	-5.0	-10.0
4	21.3	F	41.7	18.0	*	0.5		*	R	*	*	*	*	*	*	10.0	0.0	0.0	-5.0	*	5.0	-10.0	-5.0	-5.0	-20.0
									L	*	*	*	*	*	*	5.0	5.0	5.0	5.0	*	-5.0	-10.0	-5.0	-5.0	0.0
5	32.5	M	55.0	13.6	8.0	0.5	5.6	1.7	R	-13.0	-8.0	-4.0	-10.0	0.0	0.0	5.0	-5.0	0.0	-5.0	-5.0	0.0	0.0	-5.0	-5.0	0.0
									L	3.5	-1.0	0.0	-10.5	-2.0	-2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-5.0
6	29.2	F	51.8	14.5	16.9	1.3	6.2	0.9	R	-11.0	1.0	-13.0	6.0	-4.5	-6.0	-5.0	-5.0	-15.0	0.0	0.0	0.0	0.0	-5.0	-5.0	0.0
									L	-6.5	-5.0	2.0	-2.0	-7.0	-4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-5.0	-5.0	-10.0
7	18.6	F	54.3	13.8	7.2	0.9	7.3	2.1	R	-4.5	-10.0	-1.5	-15.0	1.0	-4.5	0.0	0.0	-15.0	-10.0	0.0	5.0	-5.0	0.0	-10.0	5.0
									L	-6.0	0.0	-8.5	-11.0	-8.5	0.0	-5.0	-5.0	-10.0	-10.0	-10.0	-10.0	-15.0	-5.0	-15.0	0.0
8	29.5	F	54.0	13.9	17.7	0.9	5.4	0.8	R	*	*	*	*	*	*	10.0	-5.0	-10.0	0.0	-5.0	5.0	-5.0	5.0	0.0	0.0
									L	*	*	*	*	*	*	-5.0	5.0	-10.0	0.0	0.0	-5.0	-5.0	-5.0	-5.0	10.0
9	30.1	F	53.0	14.2	30.9	0.9	4.5	0.4	R	-4.0	-3.5	-5.0	-7.5	0.0	9.5	-5.0	0.0	0.0	0.0	10.0	10.0	0.0	10.0	0.0	0.0
									L	-1.0	-2.5	0.0	-3.0	-7.0	-7.0	-10.0	0.0	-5.0	-5.0	0.0	-10.0	-15.0	-5.0	10.0	10.0

ID	Age (yrs.)	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
12	42	F	69.0	14.5	4.6	0.5	7.0	3.3	R	-11.0	-6.0	-23.0	-8.0	-36.0	-34.5	-5.0	-5.0	-15.0	-15.0	-45.0	-55.0	-70.0	-65.0	-60.0	-50.0
									L	-1.0	0.0	1.5	2.5	-4.0	-3.5	15.0	10.0	10.0	0.0	10.0	0.0	-15.0	-15.0	-20.0	0.0
15	41.1	F	37.0	13.5	*	0.5		*	R	-6.0	0.5	-14.0	-11.0	-6.0	0.0	0.0	0.0	-10.0	-10.0	5.0	5.0	-10.0	-10.0	0.0	-5.0
									L	-0.5	-5.0	-5.5	-5.5	-20.0	-1.5	0.0	-15.0	-10.0	-10.0	0.0	-15.0	-10.0	-10.0	-15.0	0.0
16	40.4	M	61.6	12.0	5.0	0.5	6.6	2.5	R	-7.0	-2.5	-5.0	-8.0	-10.0	-2.0	0.0	0.0	10.0	0.0	0.0	-15.0	0.0	-10.0	0.0	-10.0
									L	-10.0	-4.0	0.0	1.0	-14.0	-5.0	10.0	-5.0	0.0	5.0	0.0	0.0	-30.0	0.0	0.0	0.0
Mean	31.8		53.5	14.1	18.2	2.4	7.2	1.3		-4.5	-3.0	-5.4	-7.1	-8.2	-3.4	1.0	-0.7	-3.6	-4.3	-3.7	-4.0	-8.6	-7.1	-8.1	-4.8
STD	8.3		8.7	1.5	17.4	4.6	2.5	1.1		6.0	3.7	7.0	6.8	9.4	9.9	6.2	5.1	9.1	5.8	11.6	13.4	15.2	14.3	13.9	12.8
Max	18.6		37.0	12.0	4.6	0.5	4.5	0.3		-13.0	-10.0	-23.0	-21.0	-36.0	-34.5	-10.0	-15.0	-15.0	-15.0	-45.0	-55.0	-70.0	-65.0	-60.0	-50.0
Min	42.0		69.0	18.0	55.2	15.7	13.0	3.3		10.0	3.0	2.0	6.0	1.0	10.0	15.0	10.0	15.0	5.0	10.0	10.0	0.0	10.0	10.0	10.0
Med	30.1		54.0	13.9	12.4	0.9	6.6	0.8		-6.0	-2.5	-5.0	-8.0	-6.0	-2.0	0.0	0.0	-5.0	0.0	0.0	0.0	-5.0	-5.0	-5.0	0.0

Note: * indicating missing data, either due to haemolysis with regards to the pharmacokinetic data, or equipment issues/SNR discrepancy (DPOAEs) and tester errors (PTA at 9 kHz); Yellow shading indicates the limits of the audiometer.

Table 6.16

Week 2 Pharmacokinetic Results and Change in Audiology Results from Baseline for capreomycin (Audiology Baseline minus Week 2: Right and Left ears, n = 4)

8	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.1	F	60.0	16.7	*	0.5	*	*	R	0.0	-13.0	0.0	2.0	6.0	-15.0	5.0	0.0	0.0	5.0	0.0	5.0	-35.0	-30.0	0.0	0.0
									L	6.0	-1.0	1.5	0.0	-8.0	0.0	0.0	-5.0	5.0	5.0	0.0	0.0	-5.0	0.0	0.0	0.0
14	22.4	F	43.0	17.4	*	0.5	*	*	R	-0.5	-2.5	5.5	4.5	-13.0	-4.0	-5.0	0.0	0.0	-5.0	-5.0	-10.0	-5.0	-15.0	-10.0	-10.0
									L	-1.0	-4.0	-6.5	-7.0	0.5	-10.5	0.0	0.0	10.0	-10.0	0.0	-5.0	-5.0	-10.0	-35.0	-30.0
17	38.2	F	42.8	11.7	42.6	0.5	3.5	0.3	R	-12.0	-5.0	-6.0	1.0	-3.0	-4.5	0.0	-5.0	0.0	0.0	0.0	5.0	5.0	-5.0	-5.0	0.0
									L	-3.0	-3.0	-7.0	-8.5	4.5	0.0	0.0	-5.0	0.0	0.0	0.0	0.0	-30.0	0.0	0.0	0.0
18	37.1	F	72.4	13.8	5.6	0.4	6.1	2.5	R	-2.0	-2.0	*	*	-1.5	*	-5.0	-5.0	0.0	-5.0	-10.0	-10.0	-10.0	-5.0	-10.0	-15.0
									L	-8.0	-8.0	-7.0	-5.0	0.0	-1.0	5.0	-10.0	-10.0	0.0	-10.0	-10.0	-10.0	-20.0	-10.0	0.0
Mean	32.1		53.8	14.3	16.8	1.9	6.7	1.3		-4.1	-3.7	-4.4	-5.2	-6.3	-4.0	1.0	-1.7	-3.0	-3.2	-3.4	-3.7	-10.2	-7.8	-8.0	-5.2
STD	7.8		9.9	1.8	16.8	4.0	2.5	1.1		5.8	3.7	6.3	6.6	8.8	8.5	5.8	4.8	8.1	5.8	9.8	11.6	14.8	13.1	13.0	12.0
Min	18.6		52.8	14.2	55.2	15.7	13.0	0.3		10.0	3.0	5.5	6.0	6.0	10.0	15.0	10.0	15.0	5.0	10.0	10.0	5.0	10.0	10.0	10.0

8	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
Max	42.0		72.4	18.0	55.2	15.7	13.0	3.3		-13.0	-13.0	-23.0	-21.0	-36.0	-34.5	-10.0	-15.0	-15.0	-15.0	-45.0	-55.0	-70.0	-65.0	-60.0	-50.0
Med	32.5		54.0	13.9	8.0	0.5	6.2	0.8		-4.3	-3.3	-5.0	-5.5	-5.3	-3.5	0.0	0.0	0.0	0.0	0.0	0.0	-5.0	-5.0	-5.0	0.0

Note: *indicating missing data, either due to haemolysis with regards to the pharmacokinetic data or due to equipment issues/SNR discrepancy (DPOAEs), Yellow shading indicates the limits of the audiometer.

6.3.1.3. Week 4 – study visit T2.

The participants' pharmacokinetic readings and their change in hearing from baseline at week four are described in Table 6.17 (kanamycin participants) and 6.18 (capreomycin participants).

Dropout from baseline was 11 participants, and thus 11 participants were present at week 4 (n = 11). At week 4, the mean age shifted to 29.3 years, in comparison to 33.78 years at baseline. The mean weight also shifted slightly to 55.88 kg at week four compared to 54.13 kg at baseline. Three of these 11 participants were using capreomycin as the injectable by week 4.

The mean dose of kanamycin was 13.7 mg/kg (SD ± 2.1) and of capreomycin was 15.3 mg/kg (SD ± 3.9). Peak levels for kanamycin and capreomycin were 11.1 μg/mg (SD ± 7.9) and 6.4 μg/mg (SD ±2.1) respectively. The peak levels dropped from the previous study visit, particularly with capreomycin. Trough levels also dropped from the previous study visit, yet not to the same extent to 1.4 μg/mg (SD ±1.5) and 0.5 μg/mg (SD ±0) respectively. The half-life was 7.2 hours (SD ±1.5) for kanamycin and 6.3 hours (SD ±0.8) for capreomycin. The volume of distribution was 2.3 ℓ/kg (SD ± 1.5) for kanamycin and 2.2 ℓ/kg (SD ± 0.1) for capreomycin.

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 2 kHz, 8 kHz, 10 kHz and 12 kHz of -6.8 dB (SD ±5.4), -6.7 dB (SD ±7.6), -8.7 dB (SD± 6.4) and -6.4 dB (SD ±7.1) respectively. There were significant individual changes at all the other frequencies (4 kHz and 6 kHz), yet not a mean significant change. There was a mean significant change (10 dB) noted in the PTA at 12.5 kHz, 14 kHz and 16 kHz of -10 dB (SD ±16.2), -15.4 dB (SD ±16.3) and -13.1 dB (SD ±18.3) respectively (see Table 6.17).

For those participants taking capreomycin, a mean significant change of DPOAEs was noted at 4 kHz and 10 kHz of -6 dB (SD ±5) and -12.7 dB (SD ±3.1) respectively and at 9

kHz, 10 kHz. 11.2 kHz and 12.5 kHz of -13.3 dB (SD ± 11.5), -16.7 dB (SD ± 14.4), -16.7 dB (SD ± 25.7) and -15 dB (SD ± 21.8) respectively (see Table 6.18).

Table 6.17

Week 4 Pharmacokinetic Results of kanamycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 4: Right and Left ears, n = 8)

IID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
1	24.5	F	51.7	10.6	3.7	0.1	4.5	2.7	R	-19.5	-3.0	-7.0	-20.0	-9.0	-9.0	-5.0	5.0	0.0	-10.0	0.0	-5.0	-30.0	-50.0	-45.0	-5.0
									L	-7.0	-8.0	-8.5	-1.0	-13.0	-6.0	0.0	-5.0	0.0	-5.0	0.0	-5.0	-5.0	-10.0	-15.0	-60.0
4	21.3	F	42.1	17.8	5.8	0.9	9.2	3.5	R	-2.0	-4.0	-3.5	-12.0	-4.0	-5.0	0.0	0.0	-5.0	-5.0	0.0	0.0	-5.0	0.0	-5.0	-5.0
									L	-3.0	-1.0	4.0	-1.0	-5.5	-2.5	0.0	5.0	10.0	10.0	5.0	0.0	0.0	0.0	-5.0	0.0
5	32.5	M	56.3	13.3	14.8	1.0	6.1	0.9	R	-13.5	-6.0	-20.0	-8.0	0.0	0.0	0.0	0.0	-15.0	-15.0	-5.0	-5.0	-10.0	-10.0	-5.0	0.0
									L	-3.0	5.0	-5.5	-9.0	-20.0	-18.0	0.0	5.0	0.0	0.0	-30.0	-20.0	-25.0	-25.0	-25.0	-35.0
6	29.2	F	51.8	14.5	26.2	2.1	6.3	0.6	R	-7.5	-1.0	-6.0	8.0	-6.0	-7.5	0.0	-5.0	0.0	-5.0	0.0	5.0	-5.0	-10.0	-35.0	0.0
									L	-1.0	-7.5	1.5	-2.5	-5.5	-1.0	-5.0	-5.0	5.0	0.0	0.0	0.0	0.0	-5.0	-20.0	-30.0
7	18.7	F	54.0	13.9	13.6	0.9	5.9	1.0	R	-7.0	-9.0	-1.5	-18.5	-16.5	-13.5	*	*	*	*	*	*	*	*	*	*
									L	-7.0	-1.0	-1.0	-5.5	-20.0	-3.5	*	*	*	*	*	*	*	*	*	*
8	29.5	F	54.0	13.9	5.7	1.0	8.4	2.8	R	-4.0	-11.0	-8.5	-13.0	0.0	-7.5	5.0	-5.0	5.0	5.0	0.0	10.0	-10.0	15.0	5.0	-5.0
									L	-3.0	4.5	-6.0	2.0	-3.0	-11.5	-10.0	15.0	-5.0	5.0	-15.0	-5.0	-5.0	-5.0	0.0	5.0
9	30.2	F	54.0	13.9	7.7	5.0	35.6	4.8	R	-10.0	-0.5	-3.5	-9.0	-10.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.0	-5.0	-10.0
									L	-1.0	-0.5	-1.0	-2.0	-11.0	-17.0	0.0	0.0	0.0	5.0	5.0	-10.0	-5.0	-10.0	-40.0	-15.0
16	40.5	M	59.4	12.0	*	0.5	*	*	R	-13.5	-3.0	-9.0	-9.0	-6.5	-4.0	-10.0	0.0	10.0	-15.0	0.0	-5.0	-20.0	-25.0	-5.0	-10.0
									L	-9.0	-6.0	0.0	1.0	-8.5	-1.0	0.0	-15.0	-15.0	50.0	0.0	0.0	0.0	0.0	-10.0	0.0

IID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
Mean	28.3		55.4	13.7	11.1	1.4	7.2	2.3		-6.8	-3.1	-5.0	-6.7	-8.7	-6.4	-1.9	0.8	0.4	-2.3	-3.1	-3.1	-9.2	-10.0	-15.4	-13.1
STD	6.8		2.7	2.1	7.9	1.5	1.5	1.5		5.4	4.6	5.6	7.6	6.4	7.1	4.3	5.7	6.6	7.8	9.5	7.2	9.8	16.2	16.3	18.3
Max	18.7		54.0	10.6	3.7	0.1	5.9	0.6		-19.5	-11.0	-20.0	-20.0	-20.0	-18.0	-10.0	-5.0	-15.0	-15.0	-30.0	-20.0	-30.0	-50.0	-45.0	-60.0
Min	40.5		59.4	17.8	26.2	5.0	9.2	4.8		-1.0	5.0	4.0	8.0	0.0	10.0	5.0	15.0	10.0	10.0	5.0	10.0	0.0	15.0	5.0	5.0
Med	29.4		54.0	13.9	7.7	1.0	6.3	2.7		-7.0	-3.0	-5.5	-8.0	-6.5	-6.0	0.0	0.0	0.0	0.0	0.0	-5.0	-5.0	-10.0	-5.0	-5.0

Note: * indicating missing data, either due to haemolysis with regards to the pharmacokinetic data, or participant variables (PTA), Yellow shading indicates the limits of the audiometer.

Table 6.18

Week 4 Pharmacokinetic Results of capreomycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 4: Right and Left ears, n = 3)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.2	F	58.0	17.2	7.9	0.5	5.7	2.2	R	-1.0	-0.5	-1.0	-2.0	-11.0	-17.0	0.0	0.0	0.0	5.0	5.0	-10.0	-5.0	-10.0	-40.0	-15.0
									L	1.0	-11.0	-1.5	-7.5	-16.0	-15.0	5.0	0.0	5.0	-5.0	-20.0	-25.0	-45.0	-40.0	5.0	0.0
14	22.5	F	41.9	17.9	*	0.5	*	*	R	-9.0	-1.0	5.5	-2.0	-12.0	0.0	5.0	5.0	15.0	-5.0	-20.0	-25.0	-10.0	0.0	5.0	5.0
									L	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
17	38.2	F	46.4	10.8	4.9	0.5	6.9	2.3	R	-8.0	-6.0	-10.0	0.5	-10.0	8.5	-5.0	0.0	0.0	0.0	0.0	0.0	5.0	-5.0	0.0	0.0
									L	-7.5	-3.0	-5.0	-7.5	1.5	0.0	0.0	5.0	0.0	-10.0	-5.0	0.0	0.0	-10.0	0.0	0.0
Mean	32.0		58.0	15.3	6.4	0.5	6.3	2.2		-5.3	-6.0	-2.0	-3.0	-12.7	-2.2	1.7	1.7	6.7	-3.3	-13.3	-16.7	-16.7	-15.0	3.3	1.7
STD	8.3		58.0	3.9	2.1	0.0	0.8	0.1		5.5	5.0	7.8	4.1	3.1	11.9	5.8	2.9	7.6	2.9	11.5	14.4	25.7	21.8	2.9	2.9
Max	22.5		58.0	10.8	4.9	0.5	5.7	2.2		-9.0	-11.0	-10.0	-7.5	-16.0	-15.0	-5.0	0.0	0.0	-5.0	-20.0	-25.0	-45.0	-40.0	0.0	0.0
Min	38.2		58.0	17.9	7.9	0.5	6.9	2.3		1.0	-1.0	5.5	0.5	-10.0	8.5	5.0	5.0	15.0	0.0	0.0	0.0	5.0	0.0	5.0	5.0
Med	35.2		58.0	17.2	6.4	0.5	6.3	2.2		-8.0	-6.0	-1.5	-2.0	-12.0	0.0	5.0	0.0	5.0	-5.0	-20.0	-25.0	-10.0	-5.0	5.0	0.0

Note: * indicating missing data, either due to haemolysis with regards to the pharmacokinetic data, or equipment issues/SNR discrepancy (DPOAEs), or participant variables (PTA). Yellow shading indicates the limits of the audiometer.

6.3.1.4. Week 6 – study visit T3.

The participant's pharmacokinetic readings and their change in hearing from baseline at week six are described in Table 6.19 (kanamycin participants) and 6.20 (capreomycin participants).

Dropout from baseline was 13 participants, and thus nine participants were present at week 6 (n = 9). The mean age shifted slightly to 31.61 years, in comparison to 33.78 years at baseline. The total mean weight (kanamycin and capreomycin) also shifted slightly to 50, 35 kg at week 6 compared to 54.13 kg at baseline. Although the sample size is different, mean weight appeared to be dropping.

Four of these nine participants were now taking capreomycin as their injectable by week 6. The mean dose of kanamycin was 14.9 mg/kg (SD ± 2.3) and of capreomycin was 13.5 mg/kg (SD ± 3.2). Peak levels for kanamycin and capreomycin were 10.2 μg/mg (SD ± 3.1) and 5.9 μg/mg (SD ±1.3) respectively. The peak levels dropped from the previous study visit. Trough levels were 1.6 μg/mg (SD ±1.9) and 0.5μg/mg (SD ±0.1) respectively. The half-life was 13.3 hours (SD ±10.3) for kanamycin and 6.2 hours (SD ±0.8) for capreomycin. The volume of distribution was 2.2 ℓ/kg (SD ± 1.0) for kanamycin and 2.7 ℓ/kg (SD ± 1.3) for capreomycin.

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 8 kHz, 10 kHz and 12 kHz of -9.5 dB (SD ±8.8), -7.1 dB (SD±4.6) and -6.8 dB (SD±7) respectively. The frequency of 2 kHz appeared to have improved from the previous study visit and was not significant. There was a mean significant change (10 dB) noted in the PTA at 11.2 kHz, 14 kHz and 16 kHz of -10 dB (SD ±8.8), -15.5 dB (SD ±10.7) and -13 dB (SD ±18.3) respectively (see Table 6.19). The frequency 12 kHz improved and was not significant this study visit.

For those participants taking capreomycin, a mean significant change of DPOAEs was noted at 2 kHz, 4 kHz, 6 kHz, 10 kHz and 12 kHz of -9.3 dB (SD ±5.5), -7.8 dB (SD ±5.6), -8.2 dB (SD ±10.7), -10.6 dB (SD ±7.1) and -6.2 dB (SD ±6.4) respectively and at 10 kHz, 11.2 kHz and 12.5 kHz of -15.6 dB (SD ±12.1), -13.1 dB (SD ±16.2), and -15 dB (SD ±11) respectively (see Table 6.20).

Table 6.19

Week 6 Pharmacokinetic Results of kanamycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 6: Right and Left ears, n=5)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
4	21.4	F	40.0	18.8	6.9	0.9	7.8	3.0	R	-3.5	-9.0	0.0	-12.0	-6.0	-12.5	5.0	0.0	0.0	-5.0	0.0	0.0	-5.0	-10.0	-5.0	-5.0
									L	-3.5	3.5	3.0	-1.0	-7.5	-7.5	0.0	0.0	0.0	5.0	-5.0	0.0	-10.0	-5.0	-5.0	0.0
5	32.6	M	55.0	13.6	13.1	1.0	6.0	1.1	R	-12.0	-7.0	-23.0	-30.0	0.0	0.0	5.0	-5.0	-20.0	-10.0	0.0	0.0	-5.0	0.0	0.0	0.0
									L	4.5	1.0	0.0	-4.0	-15.5	-17.5	0.0	0.0	0.0	0.0	-15.0	-15.0	-25.0	-20.0	-30.0	-35.0
7	18.7	F	50.2	14.9	10.6	4.9	20.6	2.5	R	-8.0	-10.0	0.5	-16.0	-10.5	-5.0	-5.0	-5.0	-10.0	-10.0	-15.0	-10.0	-15.0	-10.0	-25.0	-55.0
									L	-5.0	0.0	-7.5	-3.5	-9.0	2.0	-5.0	-5.0	-15.0	-5.0	-5.0	-10.0	-5.0	0.0	-10.0	-10.0
8	29.6	F	54.0	13.9	*	0.5	*	*	R	-3.0	-3.0	-5.5	-12.0	-4.5	-15.0	0.0	0.0	0.0	5.0	-10.0	0.0	-25.0	-20.0	-30.0	0.0
									L	-9.5	-2.0	-3.0	-1.5	-3.0	-9.5	0.0	0.0	0.0	0.0	-10.0	5.0	-5.0	-5.0	-15.0	0.0
9	30.2	F	57.0	13.2	*	0.5	*	*	R	-11.0	-2.5	-0.5	-9.0	-11.5	2.5	0.0	0.0	5.0	0.0	0.0	-5.0	-5.0	0.0	-15.0	-10.0
									L	-7.0	-1.5	-2.5	-5.5	-3.5	-5.5	0.0	0.0	-5.0	-5.0	0.0	0.0	0.0	-5.0	-20.0	-15.0
Mean	26.5		51.2	14.9	10.2	1.6	13.3	2.2	NA	-5.8	-3.1	-3.9	-9.5	-7.1	-6.8	0.0	-1.5	-4.5	-2.5	-6.0	-3.5	-10.0	-7.5	-15.5	-13.0
STD	6.1		6.8	2.3	3.1	1.9	10.3	1.0	NA	4.8	4.4	7.4	8.8	4.6	7.0	3.3	2.4	8.0	5.4	6.1	6.3	8.8	7.5	10.7	18.3
Max	18.7		40.0	13.2	6.9	0.5	6.0	1.1	NA	-12.0	-10.0	-23.0	-30.0	-15.5	-17.5	-5.0	-5.0	-20.0	-10.0	-15.0	-15.0	-25.0	-20.0	-30.0	-55.0
Min	-32.6		-57.0	-18.8	-13.1	-4.9	-20.6	-3.0	NA	-4.5	-3.5	-3.0	1.0	0.0	-2.5	-5.0	0.0	-5.0	-5.0	0.0	-5.0	0.0	0.0	0.0	0.0
Med	29.6		54.0	13.9	10.6	0.9	13.3	2.5	NA	-6.0	-2.3	-1.5	-7.3	-6.8	-6.5	0.0	0.0	0.0	-2.5	-5.0	0.0	-5.0	-5.0	-15.0	-7.5

Note: * indicating missing data due to haemolysis with regards to the pharmacokinetic data. Yellow shading indicates the limits of the audiometer.

Table 6.20

Week 6 Pharmacokinetic Results of capreomycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 6: Right and Left ears, n = 4)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.2	F	58.1	17.2	4.9	0.5	6.8	3.6	R	-5.0	-18.0	-2.0	-6.0	-20.0	-15.0	0.0	-10.0	0.0	0.0	-15.0	-35.0	-50.0	-35.0	0.0	0.0
									L	-19.0	-1.0	-2.5	-2.0	-12.0	0.0	-5.0	0.0	5.0	-5.0	-10.0	-30.0	-15.0	0.0	0.0	0.0
16	40.5	M	43.7	12.2	6.8	0.4	5.7	1.8	R	-9.5	-7.0	-9.0	-6.0	-20.0	-4.0	0.0	0.0	0.0	0-5	-10.0	-10.0	0.0	-20.0	-10.0	-15.0
									L	-10.5	-0.5	0.0	0.0	-13.0	-7.0	-5.0	-5.0	-10.0	-5.0	0.0	-10.0	-5.0	-10.0	0.0	-5.0
17	38.3	F	44.8	11.2	*	0.5	*	*	R	-9.0	-9.0	-32.0	-3.0	-8.0	-6.5	-20.0	-5.0	-40.0	-5.0	0.0	0.0	0.0	-10.0	-5.0	0.0
									L	-6.5	-9.0	-5.0	-6.5	-5.5	0.0	0.0	0.0	0.0	-5.0	-10.0	-5.0	-5.0	-10.0	-5.0	-5.0
18	38	F	*	*	*	*	*	*	R	-14.0	-11.0	-14.0	-14.0	-6.0	-16.0	-5.0	0.0	-5.0	-5.0	-15.0	-15.0	-15.0	-10.0	-15.0	-10.0
									L	-1.0	-7.0	-1.0	-5.0	0.0	-1.0	-5.0	-5.0	-5.0	-10.0	-15.0	-20.0	-15.0	-25.0	-10.0	-5.0
Mean	38.0		48.9	13.5	5.9	0.5	6.2	2.7	NA	-9.3	-7.8	-8.2	-5.3	-10.6	-6.2	-5.0	-3.1	-6.9	-5.0	-9.4	-15.6	-13.1	-15.0	-5.6	-5.0
STD	2.2		8.0	3.2	1.3	0.1	0.8	1.3	NA	5.5	5.6	10.7	4.2	7.1	6.4	6.5	3.7	14.1	2.9	6.2	12.1	16.2	11.0	5.6	5.3
Min	35.2		43.7	11.2	4.9	0.4	5.7	1.8	NA	-19.0	-18.0	-32.0	-14.0	-20.0	-16.0	-20.0	-10.0	-40.0	-10.0	-15.0	-35.0	-50.0	-35.0	-15.0	-15.0
Max	40.5		58.1	18.8	13.1	4.9	20.6	3.6	NA	-19.0	-18.0	-32.0	-30.0	-20.0	-17.5	-20.0	-10.0	-40.0	-10.0	-15.0	-35.0	-50.0	-35.0	-30.0	-55.0
Med	38.2		44.8	12.2	5.9	0.5	6.2	2.7	NA	-9.3	-8.0	-3.8	-5.5	-10.0	-5.3	-5.0	-2.5	-2.5	-5.0	-10.0	-12.5	-10.0	-10.0	-5.0	-5.0

Note: * indicating missing data due to haemolysis with regards to the pharmacokinetic data, Yellow shading indicates the limits of the audiometer.

6.3.1.5. Week 8 – study visit T4.

The participant's pharmacokinetic readings and their change in hearing from baseline at week eight are described in Table 6.21 (kanamycin participants) and 6.22 (capreomycin participants).

Dropout from baseline was 12 participants, and thus 10 participants were present at week 8 (n = 10). This is one participant more than the previous week where there were nine participants. At week 8, the mean age shifted to 30, 75 years, in comparison to 33.78 years at baseline. The total mean weight also shifted slightly to 52.25kg at week 8.

Half of the participants present at week 8 were using capreomycin as the injectable. The mean dose of kanamycin was 14.8 mg/kg (SD ± 2) and of capreomycin was 13.9 mg/kg (SD ± 3.5). Peak levels for kanamycin and capreomycin were 34.1 μg/mg (SD ± 31.1) and 3.3 μg/mg (SD ±1.8) respectively. Trough levels were 1.7 μg/mg (SD ±1.9) and 0.5μg/mg (SD ±0.1) respectively. The half-life was 11.2 hours (SD ±9.5) for kanamycin and 9.6 hours (SD ±1.5) for capreomycin. The volume of distribution was 0.8 ℓ/kg (SD ± 0.9) for kanamycin and 6.9 ℓ/kg (SD ± 5.4) for capreomycin.

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 2 kHz, 6 kHz, 8 kHz, 10 kHz and 12 kHz of -7.7 dB (SD ±4.1), -6.6d B (SD±7.4), -9.8 dB (SD ±6.3), -6.1 (SD ±6.3) and -6.0 (SD ±8.1) respectively. There was a mean significant change (10 dB) noted in the PTA at 14 kHz and 16 kHz of -18 dB (SD ±17.2) and -16 dB (SD ±17.3) respectively (see Table 6.21). The 11.2 kHz mean response improved from the previous study visit.

For those participants taking capreomycin, a mean significant change of DPOAEs was noted at 2 kHz, 4 kHz, 6 kHz, 8 kHz, 10 kHz and 12 kHz of -9.7 dB (SD ±6.5), 12.6 dB (SD ±8.9), 11.4 dB (SD ±11.3), -7.6 dB (SD ±7.7), -16 dB (SD ±9.6) and -7.1 dB (SD ±7.9) respectively. The significant changes were not solely a deterioration of cochlear function, but

in some instances, an improvement. With regards to PTA at 6 kHz, 9 kHz, 10 kHz, 11.2 kHz and 12.5 kHz changes of -12.5 dB (SD ±20.5), -11.3 dB (SD ±14.3), -20 dB (SD ±19.8), -19.4 dB (SD ±15.9) and -16.3 dB (SD ±15.3) respectively (see Table 6.22). These pure tone results do not correlate entirely with the PTA, and DPOAEs showed improvement at 6 kHz where PTA showed deterioration.

Table 6.21

Week 8 Pharmacokinetic Results of kanamycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 8: Right and Left ears, n = 5)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
4	21.4	F	41.1	18.3	40.5	0.9	3.4	0.4	R	-4.5	-8.0	-2.5	-13.0	-8.0	-6.0	0.0	0.0	0.0	-5.0	0.0	0.0	-5.0	0.0	0.0	-15.0
									L		-1.0	1.0	-19.5	-5.5	-2.5	0.0	0.0	-5.0	-10.0	0.0	0.0	-5.0	0.0	-10.0	0.0
5	32.6	M	55.0	13.6	12.1	5.0	17.9	1.8	R	-13.0	-8.0	-21.0	-9.5	0.0	0.0	5.0	0.0	-15.0	-5.0	-5.0	-5.0	-10.0	-10.0	-10.0	-10.0
									L	-0.5	-14.5	-18.0	-11.5	-20.0	-20.0	0.0	-10.0	-15.0	-5.0	-25.0	-25.0	-25.0	-25.0	-25.0	-25.0
7	18.7	F	55.0	13.6	*	0.5	*	*	R	-8.0	-13.0	-1.5	-16.5	-7.0	-7.0	-5.0	-5.0	-5.0	-5.0	-5.0	0.0	-5.0	-5.0	-50.0	-50.0
									L	-10.0	-5.5	-0.5	-6.5	-6.0	3.0	-5.0	-5.0	-5.0	-10.0	0.0	0.0	0.0	-5.0	0.0	-25.0
8	29.6	F	52.0	14.4	*	0.5	*	*	R	-9.0	-5.0	-8.5	-12.0	-3.0	-15.0	5.0	0.0	-5.0	10.0	-10.0	0.0	-30.0	-30.0	-35.0	5.0
									L	-3.0	0.5	-5.0	2.0	-6.0	-6.5	5.0	5.0	0.0	5.0	-15.0	-10.0	-10.0	0.0	-10.0	5.0
9	30.3	F	54.0	13.9	56.1	1.5	4.4	0.2	R	-11.0	-3.5	-6.5	-8.0	-9.0	2.5	-5.0	0.0	0.0	0.0	0.0	0.0	-5.0	5.0	-5.0	-15.0
									L	-10.0	-0.5	-3.0	-3.0	4.0	-17.0	0.0	0.0	0.0	5.0	0.0	5.0	0.0	-15.0	-35.0	-30.0
Mean	27.8		54.0	14.8	34.1	1.7	11.2	0.8	NA	-7.7	-5.9	-6.6	-9.8	-6.1	-6.9	0.0	-1.5	-5.0	-2.0	-6.0	-3.5	-9.5	-8.5	-18.0	-16.0
STD	6.2		1.4	2.0	31.1	1.9	9.5	0.9	NA	4.1	5.1	7.4	6.3	6.3	8.1	4.1	4.1	5.8	6.7	8.4	8.5	10.1	11.6	17.2	17.3
Max	18.7		52.0	13.6	12.1	0.5	4.4	0.2	NA	-13.0	-14.5	-21.0	-19.5	-20.0	-20.0	-5.0	-10.0	-15.0	-10.0	-25.0	-25.0	-30.0	-30.0	-50.0	-50.0
Min	32.6		55.0	18.3	56.1	5.0	17.9	1.8	NA	-0.5	0.5	1.0	2.0	4.0	3.0	5.0	5.0	0.0	10.0	0.0	5.0	0.0	5.0	0.0	5.0
Med	30.0		54.5	13.9	34.1	0.9	11.2	0.4	NA	-9.0	-5.3	-4.0	-10.5	-6.0	-6.3	0.0	0.0	-5.0	-5.0	-2.5	0.0	-5.0	-5.0	-10.0	-15.0

Note: * indicating missing data due to haemolysis with regards to the pharmacokinetic dat

Table 6.22

Week 8 Pharmacokinetic Results of capreomycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 8: Right and Left ears, n = 5)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.3	F	55.9	17.9	*	0.5	*	*	R	-7.0	-18.0	-6.0	-12.5	-20.0	-15.0	0.0	-10.0	0.0	0.0	-15.0	-30.0	-45.0	-35.0	0.0	0.0
									L	-2.0	-1.0	-2.5	-2.0	-12.0	0.0	-5.0	0.0	0.0	-5.0	-15.0	-35.0	-20.0	0.0	5.0	0.0
14	22.6	F	41.9	17.8	2.1	0.5	10.7	10.7	R	-11.5	-8.5	-1.5	-1.5	-18.0	-6.0	*	*	*	*	*	*	*	*	*	*
									L	-11.5	-10.5	-17.5	-10.0	-17.0	-22.0	*	*	*	*	*	*	*	*	*	*
16	40.6	M	59.4	12.6	4.6	0.7	8.5	3.1	R	-10.0	-4.0	-9.0	-5.5	-5.5	-4.0	-10.0	5.0	0.0	0.0	0.0	0.0	-10.0	-20.0	-5.0	-5.0
									L	-7.0	-4.5	0.0	0.0	-9.5	-0.5	-5.0	-10.0	-5.0	-10.0	0.0	0.0	-5.0	0.0	-20.0	-5.0
17	38.3	F	44.8	11.2	*	0.5	*	*	R	-11.0	-20.5	-32.0	-21.5	-27.5	-6.5	-20.0	-10.0	-45.0	-25.0	-20.0	-20.0	-15.0	-20.0	-10.0	0.0
									L	-23.5	-23.5	-27.0	-3.5	-20.5	0.0	5.0	-25.0	-45.0	-5.0	0.0	-20.0	-20.0	-10.0	10.0	-5.0
18	38.1	F		*	*	*	*	*	R	-13.0	-26.5	-16.0	-18.5	-30.5	-16.0	0.0	-15.0	-10.0	-20.0	-40.0	-55.0	-40.0	-40.0	-40.0	-20.0
									L	0.0	-9.0	-2.0	-1.0	0.5	-1.0	0.0	-5.0	5.0	0.0	0.0	0.0	0.0	-5.0	-10.0	0.0
Mean	35.0		50.5	13.9	3.3	0.5	9.6	6.9		-9.7	-12.6	-11.4	-7.6	-16.0	-7.1	-4.4	-8.8	-12.5	-8.1	-11.3	-20.0	-19.4	-16.3	-8.8	-4.4
STD	7.2		8.5	3.5	1.8	0.1	1.5	5.4		6.5	8.9	11.3	7.7	9.6	7.9	7.8	9.2	20.5	9.6	14.3	19.8	15.9	15.3	15.8	6.8
Max	22.6		41.9	11.2	2.1	0.5	8.5	3.1		-23.5	-26.5	-32.0	-21.5	-30.5	-22.0	-20.0	-25.0	-45.0	-25.0	-40.0	-55.0	-45.0	-40.0	-40.0	-20.0
Min	40.6		59.4	17.9	4.6	0.7	10.7	10.7		0.0	-1.0	0.0	0.0	0.5	0.0	5.0	5.0	5.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0
Med	38.1		50.4	12.6	3.3	0.5	9.6	6.9		-10.5	-9.8	-7.5	-4.5	-17.5	-5.0	-2.5	-10.0	-2.5	-5.0	-7.5	-20.0	-17.5	-15.0	-7.5	-2.5

Note: * indicating missing data, either due to haemolysis with regards to the pharmacokinetic data, or participant variables (PTA)

6.3.1.6. Week 10 – study visit 5.

The participant's pharmacokinetic readings and their change in hearing from baseline at week 10 are described in Table 6.23 (kanamycin participants) and 6.24 (capreomycin participants).

Dropout from baseline was 15 participants, and thus 7 participants were present at week 10 (*n* = 7). At week 10, the mean age was 29.49 years. The total mean weight also shifted slightly to 55.52 kg at week 10.

Two of these 7 participants were using capreomycin as the injectable. The others that had been using capreomycin had dropped out. The mean dose of kanamycin was 13.5 mg/kg (SD ± 1) and of capreomycin was 17.8 mg/kg (SD ± 0). Peak levels for kanamycin were 41.2 μg/mg (SD ± 15.4), with trough levels at 0.9 μg/mg (SD ±0.6). With kanamycin, the half-life was 5 hours (SD ±0.6), and volume of distribution was 0.4 ℓ/kg (SD ±0.2). Due to too little blood that reached the laboratory, only the trough was measured at 0.5 μg/mg for capreomycin. The peak levels, half-lives and volume of distribution were not obtained.

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 2 kHz, 6 kHz, 8 kHz, 10 kHz and 12 kHz of -8.1 dB (SD ±4.5), -6.5 dB (SD±8.9), -10.2 dB (SD ±5), -8.4 (SD ±6.2) and -9.1 (SD ±10.6) respectively. There was a mean significant change (10 dB) noted in the PTA at 11.2 kHz, 12.5 kHz, 14 kHz and 16 kHz of -12.5 dB (SD ±18.4), -15.5 dB (SD ±19.4), -19 dB (SD ±19.1) and -13 dB (SD ±17.5) respectively (see Table 6.23).

For those participants taking capreomycin, a mean significant change of DPOAEs was noted at 2 kHz, 4 kHz, 8 kHz, 10 kHz and 12 kHz of -6.5 dB (SD ±6.2), -11.4 dB (SD ±10.1), -9.3 dB (SD ±8.1), -10.7 dB (SD ±10.1) and -8 dB (SD ±8.7) respectively. With regards to PTA at 8 kHz, 9 kHz, 10 kHz, 11.2 kHz and 12.5 kHz changes of -15 dB (SD ± 14.7), -27.5

dB (SD ±18.5), -32.5 dB (SD ±16.8), -25 dB (SD ±16.8) and -17.5 dB (SD ±15.5)

respectively (see Table 6.24).

Table 6.23

Week 10 Pharmacokinetic Results of kanamycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 10: Right and Left ears, n = 5)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
4	21.5	F	50.2	14.9	*	0.5	*	*	R	-9.5	-8.0	-0.5	-16.0	-11.0	-12.0	0.0	-5.0	0.0	-5.0	-5.0	-5.0	-10.0	-10.0	0.0	0.0
									L	-6.0	-1.5	3.0	-8.0	-13.5	-2.5	-5.0	-5.0	0.0	0.0	-5.0	-5.0	0.0	0.0	-15.0	0.0
5	32.7	M	59.0	12.7	*	0.5	*	*	R	-12.0	-11.0	-23.0	-10.0	0.0	0.0	0.0	-5.0	-20.0	-10.0	-5.0	0.0	-10.0	-10.0	-10.0	0.0
									L	-1.5	-4.0	-20.0	-15.0	-22.0	-20.0	-5.0	-5.0	-25.0	-20.0	-35.0	-40.0	-45.0	-50.0	-50.0	-30.0
7	18.8	F	57.0	13.2	*	0.5	*	*	R	-11.0	-13.0	1.5	-13.0	-8.0	-29.0	0.0	-5.0	0.0	-5.0	-5.0	-5.0	-15.0	-45.0	-55.0	-50.0
									L	-11.0	-6.5	-3.5	-5.5	-6.0	2.0	0.0	-5.0	-5.0	-5.0	-15.0	0.0	0.0	-5.0	-10.0	-30.0
8	29.7	F	53.3	14.07	30.4	1.6	5.4	0.5	R	-1.0	-4.0	-9.5	-17.0	-5.0	-15.0	-5.0	0.0	0.0	0.0	-10.0	-5.0	-45.0	-30.0	-25.0	-5.0
									L	-5.0	-3.5	-6.0	-4.0	-6.0	-14.5	-5.0	0.0	-5.0	0.0	0.0	-5.0	-5.0	-10.0	-15.0	-5.0
9	30.3	F	57.3	13.1	52.1	1.6	4.5	0.2	R	-14.0	-2.5	-6.5	-10.0	-9.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-5.0	0.0	-10.0	-10.0
									L	-10.0	0.0	0.0	-3.0	-3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10.0	5.0	0.0	0.0
Mean	26.6		55.4	13.5	41.2	0.9	5.0	0.4	NA	-8.1	-5.4	-6.5	-10.2	-8.4	-9.1	-2.0	-3.0	-5.5	-4.5	-8.0	-6.5	-12.5	-15.5	-19.0	-13.0
STD	6.1		3.6	1.0	15.4	0.6	0.6	0.2	NA	4.5	4.2	8.9	5.0	6.2	10.6	2.6	2.6	9.3	6.4	10.6	12.0	18.4	19.4	19.1	17.5
Max	18.8		50.2	12.7	30.4	0.5	4.5	0.2	NA	-14.0	-13.0	-23.0	-17.0	-22.0	-29.0	-5.0	-5.0	-25.0	-20.0	-35.0	-40.0	-45.0	-50.0	-55.0	-50.0
Min	32.7		59.0	14.9	52.1	1.6	5.4	0.5	NA	-1.0	0.0	3.0	-3.0	0.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	10.0	5.0	0.0	0.0
Med	29.7		57.0	13.1	41.2	0.5	5.0	0.4	NA	-9.8	-4.0	-4.8	-10.0	-7.0	-7.3	0.0	-5.0	0.0	-2.5	-5.0	-5.0	-7.5	-10.0	-12.5	-5.0

Note: * indicating missing data due to haemolysis with regards to the pharmacokinetic data, Yellow shading indicates the limits of the audiometer.

Table 6.24

Week 10 Pharmacokinetic Results of capreomycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 10: Right and Left ears, n = 2)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.3	F	56.3	17.8	*	0.5	*	*	R	-7.0	-13.0	-5.0	-18.0	-20.0	-15.0	0.0	0.0	0.0	-35.0	-50.0	-45.0	-50.0	-35.0	5.0	0.0
									L	-1.0	0.5	-2.5	-2.0	-12.0	0.0	0.0	10.0	0.0	-15.0	-35.0	-50.0	-20.0	0.0	0.0	0.0
18	38.1	F		*	*	*	*	*	R	-15.0	-24.0	*	*	*	-16.0	0.0	-5.0	0.0	0.0	-10.0	-10.0	-15.0	-10.0	-20.0	-20.0
									L	-3.0	-9.0	-3.0	-8.0	0.0	-1.0	0.0	-5.0	-5.0	-10.0	-15.0	-25.0	-15.0	-25.0	-10.0	0.0
Mean	36.7		56.3	17.8	*	0.5	*	*	NA	-6.5	-11.4	-3.5	-9.3	-10.7	-8.0	0.0	0.0	-1.3	-15.0	-27.5	-32.5	-25.0	-17.5	-6.3	-5.0
STD	2.0								NA	6.2	10.1	1.3	8.1	10.1	8.7	0.0	7.1	2.5	14.7	18.5	18.5	16.8	15.5	11.1	10.0
Max	35.3		56.3	17.8	0.0	0.5	0.0	0.0	NA	-15.0	-24.0	-5.0	-18.0	-20.0	-16.0	0.0	-5.0	-5.0	-35.0	-50.0	-50.0	-50.0	-35.0	-20.0	-20.0
Min	38.1		56.3	17.8	0.0	0.5	0.0	0.0	NA	-1.0	0.5	-2.5	-2.0	0.0	0.0	0.0	10.0	0.0	0.0	-10.0	-10.0	-15.0	0.0	5.0	0.0
Med	36.7		56.3	17.8		0.5			NA	-5.0	-11.0	-3.0	-8.0	-12.0	-8.0	0.0	-2.5	0.0	-12.5	-25.0	-35.0	-17.5	-17.5	-5.0	0.0

Note: * indicating missing data, either due to haemolysis with regards to the pharmacokinetic data, or equipment issues/SNR discrepancy (DPOAEs), Yellow shading indicates the limits of the audiometer.

6.3.1.7. Week 12 – study visit T6.

The participant's pharmacokinetic readings and their change in hearing from baseline at week 12 are described in Table 6.25 (kanamycin participants) and 6.26 (capreomycin participants).

Dropout from baseline was 16 participants, and thus 6 participants were present at week 12 (n = 6). Due to the reasons described above, only 6 participants completed the entire study. At week 12, the mean age was 28.08 years. The total mean weight shifted again slightly to 53.78kg at week 12.

One of these 6 participants were using capreomycin as the injectable. The others that had been using capreomycin had dropped out. The mean dose of kanamycin was 14.9 mg/kg (SD ± 2.5), and the dose of capreomycin was 18 mg/kg. Peak levels for kanamycin were 4.4 μg/mg (SD ± 2.3) with trough levels at 0.9 μg/mg (SD ±0.4). For kanamycin, the half-life was 13.7 hours (SD ±6.0), and the volume of distribution was 5.8 ℓ/kg (SD ± 5.1). Only the trough level was obtained for capreomycin at 0.5 μg/mg.

For participants taking kanamycin, a mean significant change of DPOAEs was noted at 2 kHz, 4 kHz, 6 kHz, 8 kHz, 10 kHz and 12 kHz of -11.2 dB (SD ±7.1), -8.9 dB (SD±3.4), -10.6 dB (SD ±5.9), -11.8 (SD ±4.8), -12.5 dB (SD ±6.4) and -11.7 dB (SD ±9.4) respectively. There was a mean significant change (10 dB) noted in the PTA at 9 kHz, 10 kHz, 11.2 kHz, 12.5 kHz, 14 kHz and 16 kHz of -14.6 dB (SD ±7.4), -15 dB (SD ±7.1), -22.1 dB (SD ±18.6), -17.9 dB (SD ±17.2), -19.2 dB (SD ±18) and -16.3 dB (SD ±14.7) respectively (see Table 6.25)

For the one participant taking capreomycin, a mean significant change of DPOAEs was noted at 2 kHz, 4 kHz, 8 kHz, 10 kHz and 12 kHz of -8.8 dB (SD ±2.5), -9.5 dB (SD ± 12), -10 dB (SD ±11.3), -16 dB (SD ±5.7) and -7.5 dB (SD ±10.6) respectively. With regards to PTA at 8 kHz, 9 kHz, 10 kHz, 11.2 kHz and 12.5 kHz changes of -25 dB (SD ±14.1), -42.5

dB (SD ±10.6), -47.5 dB (SD ± 3.5), -35 dB (SD ±21.2) and -17.5 dB (SD ±24.7)

respectively (see Table 6.26).

Table 6.25

Week 12 Pharmacokinetic Results of kanamycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 12: Right and Left ears, n = 5)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	V_D (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
4	21.5	F	40	18.8	*	0.5	*	*	R	-9.5	-12.0	-8.5	-13.0	-10.5	-15.0	0.0	-10.0	-10.0	-5.0	-5.0	-5.0	0.0	-10.0	-10.0	-10.0
									L	-6.0	-5.5	-8.0	-10.0	-5.5	-7.5	-5.0	-5.0	-10.0	-5.0	0.0	0.0	-5.0	-5.0	-10.0	-5.0
5	32.7	M	59	12.7	7.5	1.6	10.8	2.1	R	-13.0	-12.0	-21.5	-10.0	0.0	0.0	5.0	-5.0	-15.0	-5.0	-10.0	-5.0	-10.0	-5.0	-10.0	-5.0
									L	-11.5	-13.0	-16.0	-13.5	-22.0	-20.0	-10.0	-10.0	-5.0	-10.0	-25.0	-25.0	-35.0	-35.0	-45.0	-35.0
7	18.8	F	57	13.2	4.4	1.0	10.5	3.7	R	-8.0	-13.0	-1.5	-20.0	-17.0	-29.0	0.0	-5.0	-5.0	-10.0	-10.0	-15.0	-50.0	-50.0	-60.0	-50.0
									L	-16.0	-7.5	-6.5	-7.5	-11.0	0.0	0.0	-5.0	0.0	-5.0	-15.0	-5.0	-5.0	0.0	-5.0	-25.0
8	29.7	F	54.1	13.9	2.0	1.0	22.7	13.3	R	-4.0	-4.0	-16.5	-18.0	-14.5	-15.0	0.0	0.0	-10.0	0.0	-10.0	-10.0	-50.0	-40.0	-30.0	-10.0
									L	-12.5	-6.0	-13.0	-5.5	-7.0	-17.5	-5.0	0.0	-10.0	0.0	-10.0	-5.0	-10.0	-10.0	-15.0	-10.0
9	30.4	F	57	13.2	3.8	0.9	10.8	4.3	R	-29.0	-6.5	-16.0	-16.0	-16.0	-4.5	-10.0	0.0	-10.0	-5.0	0.0	-5.0	-15.0	-10.0	-30.0	-15.0
									L	-7.0	-8.0	-10.0	-8.0	-14.0	-17.0	0.0	0.0	-5.0	-5.0	-5.0	-10.0	-15.0	-15.0	-15.0	-25.0
Mean	26.6		53.78	14.9	4.4	0.9	13.7	5.8	NA	-11.2	-8.9	-10.6	-11.8	-12.5	-11.7	-0.8	-2.9	-6.3	-8.3	-14.6	-15.0	-22.1	-17.9	-19.2	-16.3
STD	6.1		6.89	2.5	2.3	0.4	6.0	5.1	NA	7.1	3.4	5.9	4.8	6.4	9.4	4.9	3.9	4.2	3.3	7.4	7.1	18.6	17.2	18.0	14.7
Max	18.8		40	12.7	2.0	0.5	10.5	2.1	NA	-29.0	-13.0	-21.5	-20.0	-22.0	-29.0	-10.0	-10.0	-15.0	-10.0	-25.0	-25.0	-50.0	-50.0	-60.0	-50.0
Min	32.7		59	18.8	7.5	1.6	22.7	13.3	NA	-4.0	-4.0	-1.5	-5.5	0.0	0.0	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-5.0	-5.0
Med	29.7		57	13.2	4.1	1.0	10.8	4.0	NA	-10.5	-7.8	-11.5	-11.5	-12.5	-15.0	0.0	-5.0	-10.0	-5.0	-10.0	-5.0	-12.5	-10.0	-15.0	-12.5

* indicating missing data due to haemolysis with regards to the pharmacokinetic data, Yellow shading indicates the limits of the audiometer.

Table 6.26

Week 12 Pharmacokinetic Results of capreomycin and Change in Audiology Results from Baseline (Audiology Baseline minus Week 12: Right and Left ears, n = 1)

ID	Age	Gender	Weight (kg)	Dose (mg/kg)	Peak (µg/ml)	Trough (µg/ml)	Half-life (hours)	VD (l/kg)	EAR	DPOAE (dB)						PTA (dB)									
										2 kHz	4 kHz	6 kHz	8 kHz	10 kHz	12 kHz	3 kHz	4 kHz	6 kHz	8 kHz	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
10	35.4	F	55.6	18.0	*	0.5	*	*	R	-10.5	-18.0	-6.0	-18.0	-20.0	-15.0	0.0	-5.0	0.0	-35.0	-50.0	-45.0	-50.0	-35.0	0.0	-5.0
									L	-7.0	-1.0	-4.0	-2.0	-12.0	0.0	15.0	10.0	5.0	-15.0	-35.0	-50.0	-20.0	0.0	0.0	0.0
Mean	35.4		55.6	18.0		0.5			NA	-8.8	-9.5	-5.0	-10.0	-16.0	-7.5	7.5	2.5	2.5	-25.0	-42.5	-47.5	-35.0	-17.5	0.0	-2.5
STD	NA		NA						NA	2.5	12.0	1.4	11.3	5.7	10.6	10.6	10.6	3.5	14.1	10.6	3.5	21.2	24.7	0.0	3.5
Max	35.4		55.6	18.0		0.5			NA	-10.5	-18.0	-6.0	-18.0	-20.0	-15.0	0.0	-5.0	0.0	-35.0	-50.0	-50.0	-50.0	-35.0	0.0	-5.0
Min	35.4		55.6	18.0		0.5			NA	-7.0	-1.0	-4.0	-2.0	-12.0	0.0	15.0	10.0	5.0	-15.0	-35.0	-45.0	-20.0	0.0	0.0	0.0
Med	35.4		55.6	18.0		0.5			NA	-8.8	-9.5	-5.0	-10.0	-16.0	-7.5	7.5	2.5	2.5	-25.0	-42.5	-47.5	-35.0	-17.5	0.0	-2.5

Note: * indicating missing data, due to haemolysis with regards to the pharmacokinetic data, Yellow shading indicates the limits of the audiometer.

6.3.1.8. PTA and DPOAE changes in relation to pharmacokinetics.

The significant mean PTA and DPOAE changes in relation to the pharmacokinetics of both kanamycin and capreomycin are detailed in Table 6.27 and Table 6.28. Furthermore, Table 6.29 highlights the various grading scales, together with the relevant injectables and dosages as well as the HIV status.

- **PTA and DPOAEs in relation to pharmacokinetics**

With regards to PTA (Table 6.27), the most significant changes were seen in the later weeks, particularly from T4 to T6. As described in Table 6.8 where the significant changes of kanamycin and capreomycin were detailed at weeks 10 and 12 (T4 and T6), and kanamycin showed changes in more frequencies than the capreomycin participants.

However, in Table 6.27, when not taking 3 kHz and 4 kHz into account, capreomycin appeared to be potentially more ototoxic. Yet, the sample sizes were different at the various weeks, and those on capreomycin were initially on kanamycin and were switched to capreomycin, as they were demonstrating a hearing loss. Therefore, they may have been more susceptible to hearing loss. The toxicity profile, however, was under observation of the various frequencies and decibels changes, but could not be calculated statistically due to the sample size.

The doses were similar between kanamycin and capreomycin, yet at T5, the kanamycin dose was 13.5 mg/kg with capreomycin being 17.8 mg/kg, and capreomycin displayed more toxicity than kanamycin (at these frequencies). Similarly, at T6, when looking at frequencies of 6 kHz and above, the capreomycin dosage was higher at 18 mg/kg when compared to the kanamycin dosage of 14.9 mg/kg, where capreomycin also appeared to display more toxicity. Yet, this result could be skewed as there was only one participant on capreomycin at T6. Furthermore, the trough levels for both kanamycin and capreomycin were

below 10 μg/ml and not toxic, yet ototoxicity still occurred. It is postulated that the ototoxicity is related to dosage per kg and not to trough levels.

However, this was not observed with DPOAE, as toxicity in the latter weeks were similar (weeks 10 and 12) (Table 6.28).

Table 6.27

Significant PTA changes in relation to pharmacokinetics for kanamycin and capreomycin from baseline to week 12

		T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 |(KM)	T2 (CM)	T3 | (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
N		22	0	11	4	8	3	5	4	5	5	5	2	5	1
Dropout/ CM*	**Frequency**	0	0	7	0	3	1	3	0	0	0	0	3	0	1
Mean PTA	6 kHz			-	-	-	-	-	-	-	12.5	-	-	-	-
significant changes	SD			-	-	-	-	-	-	-	20	-	-	-	-
(dB)	8 kHz			-	-	-	-	-	-	-	-	-	-15	-	-25
	SD			-	-	-	-	-	-	-	-	-	14.7	-	14.1
	9 kHz			-	-	-	-13.3	-	-	-	-11.3	-	-27.5	-14.6	-42.5
	SD			-	-	-	11.5	-	-	-	14.3	-	18.5	7.4	10.6
	10 kHz			-	-	-	-16.7	-	15.6	-	-20	-	-32.5	-15	-47.5
	SD			-	-	-	14.4	-	12.1	-	19.8	-	16.8	7.1	3.5
	11.2 kHz			-	-10.2	-	-16.7	-10	-13.1	-	-19.4	-12.5	-25	-22	-35
	SD			-	14.8	-	25.7	8.8	16.2	-	15.9	18.4	16.8	18.6	21.2
	12.5 kHz			-	-	-10	-15	-	-15	-	-16.3	15.5	-17.5	-17.9	-17.5
	SD			-	-	16.2	21.8	-	11	-	15.3	19.4	15.5	17.2	24.7
	14 kHz			-	-	-15.4	-	-15.5	-	-18	-	-19	-	-19.2	-
	SD			-	-	16.3	-	10.7	-	17.2	-	19.1	-	18	-
	16 kHz			-	-	-13.1	-	-13	-	-16	-	-13	-	-16.3	-
	SD			-	-	18.3	-	18.3	-	17.3	-	17.5	-	14.7	-

		T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 |(KM)	T2 (CM)	T3 | (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
Age (in years)	Mean	33.8		31.8	32.1	28.3	32.0	26.5	38.0	27.8	35.0	26.6	36.7	26.6	35.4
	SD	7.3		8.3	7.8	6.8	8.3	6.1	2.2	6.2	7.2	6.1	2.0	6.1	
Dose (mg/kg)	Mean	16.0		14.1	14.3	13.7	15.3	14.9	13.5	14.8	13.9	13.5	17.8	14.9	18.0
	SD	4.8		1.5	1.8	2.1	3.9	2.3	3.2	2.0	3.5	1.0		2.5	
Peak (µg/ml)	Mean	21.0		18.2	16.8	11.1	6.4	10.2	5.9	34.1	3.3	41.2		4.4	
	SD	38.6		17.4	16.8	7.9	2.1	3.1	1.3	31.1	1.8	15.4		2.3	
Trough (µg/ml)	Mean	0.4		2.4	1.9	1.4	0.5	1.6	0.5	1.7	0.5	0.9	0.5	0.9	0.5
	SD	0.3		4.6	4.0	1.5	0.0	1.9	0.1	1.9	0.1	0.6		0.4	
Half-life (hours)	Mean	7.5		7.2	6.7	7.2	6.3	13.3	6.2	11.2	9.6	5.0		13.7	
	SD	5.5		2.5	2.5	1.5	0.8	10.3	0.8	9.5	1.5	0.6		6.0	
V_D (ℓ/kg)	Mean	4.5		1.3	1.3	2.3	2.2	2.2	2.7	0.8	6.9	0.4		5.8	
	SD	5.1		1.1	1.1	1.5	0.1	1.0	1.3	0.9	5.4	0.2		5.1	

‘-‘ No significant change detected, *participant, dropped out from the study or switched to capreomycin,

Table 6.28

Significant DPOAE changes in relation to pharmacokinetics for kanamycin and capreomycin from baseline to week 12

	Frequency	T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 (KM)	T2 (CM)	T3 (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
N		22	0	11	4	8	3	5	4	5	5	5	2	5	1
Dropout/ switched to capreomycin		0	0	7	0	3	1	3	0	0	0	0	3	0	1
Mean DPOAE significant change (dB)	2 kHz			-	-	-6.8	-	-	-9.3	-7.7	-9.7	-8.1	-6.5	-8.8	-8.8
	SD			-	-	5.4	-	-	5.5	4.1	6.5	4.5	6.2	2.5	2.5
	4 kHz			-	-	-	-6	-	-7.8	-	12.6	-	-11.4	-	-9.5
	SD			-	-	-	5	-	5.6	-	8.9	-	10.1	-	12
	6 kHz			-	-	-	-	-	-8.2	-6.6	11.4	-6.5	-	-9.5	-
	SD			-	-	-	-	-	10.7	7.4	11.3	8.9	-	12	-
	8 kHz			-7.1	-	-6.7	-	-9.5	-	-9.8	-7.6	-10.2	-9.3	-10	-10
	SD			6.8	-	7.6	-	8.8	-	6.3	7.7	5	8.1	11.3	11.3
	10 kHz			-8.2	-6.3	-8.7	-12.7	-7.1	-10.6	-6.1	-16	-8.4	-10.7	-16	-16
	SD			9.4	8.8	6.4	3.1	4.6	7.1	6.3	9.6	6.2	10.1	5.7	5.7
	12 kHz			-	-	-6.4	-	-6.8	-6.2	-6	-7.1	-9.1	-8	-7.5	-
	SD			-	-	7.1	-	7	6.4	8.1	7.9	10.6	8.7	10.6	-
Age (in years)	Mean	33.8		31.8	32.1	28.3	32.0	26.5	38.0	27.8	35.0	26.6	36.7	26.6	35.4
	SD	7.3		8.3	7.8	6.8	8.3	6.1	2.2	6.2	7.2	6.1	2.0	6.1	
Dose (mg/kg)	Mean	16.0		14.1	14.3	13.7	15.3	14.9	13.5	14.8	13.9	13.5	17.8	14.9	18.0
	SD	4.8		1.5	1.8	2.1	3.9	2.3	3.2	2.0	3.5	1.0		2.5	

	Frequency	T0 (KM)	T0 (CM)	T1 (KM)	T1 (CM)	T2 (KM)	T2 (CM)	T3 (KM)	T3 (CM)	T4 (KM)	T4 (CM)	T5 (KM)	T5 (CM)	T6 (KM)	T6 (CM)
Peak (µg/ml)	Mean	21.0		18.2	16.8	11.1	6.4	10.2	5.9	34.1	3.3	41.2		4.4	
	SD	38.6		17.4	16.8	7.9	2.1	3.1	1.3	31.1	1.8	15.4		2.3	
Trough (µg/ml)	Mean	0.4		2.4	1.9	1.4	0.5	1.6	0.5	1.7	0.5	0.9	0.5	0.9	0.5
	SD	0.3		4.6	4.0	1.5	0.0	1.9	0.1	1.9	0.1	0.6		0.4	
Half-life (hours)	Mean	7.5		7.2	6.7	7.2	6.3	13.3	6.2	11.2	9.6	5.0		13.7	
	SD	5.5		2.5	2.5	1.5	0.8	10.3	0.8	9.5	1.5	0.6		6.0	
V_D (ℓ/kg)	Mean	4.5		1.3	1.3	2.3	2.2	2.2	2.7	0.8	6.9	0.4		5.8	
	SD	5.1		1.1	1.1	1.5	0.1	1.0	1.3	0.9	5.4	0.2		5.1	

‘-‘ No significant change detected.

6.3.1.9. Kanamycin and capreomycin mean dose in relation to ototoxicity.

This section describes the kanamycin and capreomycin mean dosages in relation to the ototoxicity detected by using the grading systems available (Table 6.29). Each participant has two results in the last four columns; the top result is of the right ear, while the bottom is the left ear. The gradable hearing loss is detailed according to the existing adult grading scales (according to PTA). As there is no grading scale for DPOAEs, any loss of 6 dB or greater was considered a loss and marked as 'yes' (Table 6.29).

It must be noted that in some instances, with PTA, loss of hearing is observed in the higher frequencies, yet not depicted as a gradable loss on a grading scale. Overall, significant changes were noticed more with DPOAEs than the PTA results. Patients on capreomycin did not show less of a hearing loss than those on kanamycin. However, they were often switched to capreomycin when they were experiencing ototoxicity. Their auditory system could have been vulnerable to develop hearing loss by this stage (Table 6.29).

The lowest dosage of kanamycin was 11.9 mg/kg (participant 16). This participant was switched to capreomycin (12.4 mg/kg) however at week 4. The highest dosage was 34 mg/kg of kanamycin (participant 14), but she was also switched onto capreomycin. Participant 16 shows more of a gradable hearing loss than participant 14. Also, the HIV negative participants displayed similar loss of hearing as the HIV positive patients, yet the sample was too small to make the assumption that there is no relationship between HIV status and hearing (Table 6.29).

Table 6.29

Injectable Mean Dose from Baseline and Ototoxicity Grading Scales (right and left ears)

Patient	Weeks in the Study (T)	HIV Status	Age (Baseline)	Gender	KM mean dose	CM mean dose	DPOAE 6 dB	TUNE	CTCAE	ASHA)
1	0,1,2	POS	24.4	F	13.5	NA	YES	2a	-	YES
							YES	1a	-	YES
2	0,1	POS	40.1	M	12.8	NA	-	0	-	NO
							-	1a	-	NO
4	0,1,2,3,4,5,6	POS	21.2	F	17.8	NA	YES	1a	-	YES
							YES	0	-	NO
5	0,1,2,3,4,5,6	POS	32.4	M	13.4	NA	YES	1a	-	YES
							YES	2a	-	YES
6	0,1,2	POS	29.1	F	14.2	NA	YES	0	-	YES
							YES	0	-	YES
7	0,1,2,3,4,5,6	NEG	18.6	F	13.8	NA	YES	2a	-	YES
							YES	0	-	YES
8	0,1,2,3,4,5,6	POS	29.4	F	14.2	NA	YES	2a	-	YES
							YES	1a	-	YES
9	0,1,2,3,4,5,6	POS	30.1	F	13.6	NA	YES	1a	-	YES
							YES	1a	-	YES
10	0,1,2,3,4,5,6	POS	35.1	F	15.9	17.5	YES	2a	-	YES
							YES	2a	-	YES
12	0,1	POS	41.11	F	14.5	NA	YES	2a	1	YES
							NO	1a	-	YES

Patient	Weeks in the Study (T)	HIV Status	Age (Baseline)	Gender	KM mean dose	CM mean dose	DPOAE 6 dB	TUNE	CTCAE	ASHA)
14	0,1,2,4	POS	22.4	F	34.1	17.7	YES	1a	-	YES
							YES	1a	-	YES
15	0,1,	NEG	41	F	14.1	NA	YES	1a	-	YES
							YES	1a	-	YES
16	0,1,2,3,4	POS	40.4	M	11.9	12.4	YES	2a	-	YES
							YES	1a	-	YES
17	0,1,2,3,4	POS	38.1	F	17.9	11.2	YES	2a	-	YES
							YES	1a	-	YES
18	0,1,3,4,5	POS	37.11	F	14.1	13.8	YES	1a	-	YES
							YES	2a	-	YES

Note: '‒' indicates no grade is applicable, TUNE Grading system only grades up to 12.5 kHz and does not include 9 and 11.2 kHz. CTCAE only grades up to 8 kHz. ASHA is for all the frequencies. Audiology results not included for those that dropped out before week 2. Audiology results included are at last study visit before dropout, or last audiology results available

6.3.2. Summary of Pharmacokinetics in Relation to Hearing

In summary, the sample was too small to understand the hearing loss at the various weeks in relation to the dosage and trough levels. Overall, the trough levels did not correlate to ototoxicity. In some instances, when looking at mean levels (Table 6.27 and 6.28), dosage did correlate to ototoxicity, yet when looking at individual patients, such as in Table 6.29, dosage did not correlate to ototoxicity.

Overall, the pharmacokinetic results were erratic and differed significantly between individuals. A conclusive positive or negative relationship between dosage and trough levels was not observed with the progression of hearing loss.

6.4. Feasibility Findings

Lastly, the audiological and pharmacokinetics findings assisted in determining the main aim of feasibility:

Establishing the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship with hearing levels.

This further included establishing:

- The willingness of patients to participate in a pharmacokinetic study in conjunction with hearing evaluations
- To investigate whether TDM could potentially be utilised regarding dosage adjustments of kanamycin and capreomycin

The primary aim of this study was to determine the *feasibility* of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship with hearing levels. This feasibility study was impacted by

various aspects, including the willingness of participation, issues with blood samples, quality assurance including record keeping and data management, medical management and changes in protocols and lack of resources. Furthermore, the results yielded in sections 6.2 and 6.3 regarding the pharmacokinetics of kanamycin and capreomycin in relation to hearing levels impacted the possibility of TDM of kanamycin and capreomycin.

6.4.1. Willingness to Participate and Respondent Enrolment

Participation was entirely voluntary. Participants were approached and counselled by a skilled and trained study coordinator and in some cases, assisted by a study social worker regarding the study. However, despite the potential participants identified, at both study sites, willingness to participate was poor. Of the 36 potential participants at HJH and 46 at SRH, only nine and 13 consented respectively.

Thus, despite the significant number of potential participants identified, patients were not keen to take part in this involved study, which impacted the overall results and statistical outcomes. It is important to note this for the determination of a more involved pharmacokinetic study. The reasons for refusal of participation are evident in Table 6.30. Furthermore, adherence was also an issue after enrolment.

Table 6.30

Reasons for Refusal of Participation and Dropout

Reasons for refusing to participate	HJH	SRH
• Overwhelmed by the research protocol	5	9
• Overwhelmed by the DR-TB treatment protocol	2	0
• Family members refused participation	1	1
• No reason	2	3
Reasons for dropout from the study (and likely dropout from treatment)		
• Return to work		1
• Patient decided to withdraw (no reason)	1	
• Sputum positive therefore transferred to Sizwe Tropical Disease Hospital	1	3
• Passed away		1
• Refused hospital treatment (reason unknown)	1	
• Return to 'homeland' (other provinces, neighbouring countries)		3
• Injectable discontinued due to high creatinine levels		3
• Ototoxicity: thus, investigation of bedaquiline trial		1
• Non-compliance with study procedures	1	

Many patients were extremely ill and too weak to visit the clinic for their injections. Medication adherence and infection control could not be examined conclusively as the participants were not followed when they were at home.

The study coordinator enrolled 22 participants; nine form HJH and 13 from SRH. However, only six completed the entire study. The participant genders, ages, weights and HIV statuses are described in Tables 6.31 and 6.32 below. Majority of the participants were female, on kanamycin, with mean ages between 26.5 and 38 years. Also, many of the participants were HIV positive.

Table 6.31

Description of Participants on kanamycin

		T0	T1	T2	T3	T4	T5	T6
n		22	11	8	5	5	5	5
dropout (or switched to capreomycin)		0	7	3	3	0	0	0
Gender	M	7	3	2	1	1	1	1
	F	15	8	6	4	4	4	4
Age (years)	Mean	33.8	31.8	28.3	26.5	27.8	26.6	26.6
	SD	7.3	8.3	6.8	6.1	6.2	6.1	6.1
	Min	18.6	18.6	18.7	18.7	18.7	18.8	18.8
	Max	42.8	42.0	40.5	-32.6	32.6	32.7	32.7
	Median	35.1	30.1	29.4	29.6	30.0	29.7	29.7
Weight (kg)	Mean	54.1	53.5	55.4	51.2	54.0	55.4	53.8
	SD	10.9	8.7	2.7	6.8	1.4	3.6	7.7
	Min	34.0	37.0	54.0	40.0	52.0	50.2	40.0
	Max	73.0	69.0	59.4	-57.0	55.0	59.0	59.0
	Median	54.5	54.0	54.0	54.0	54.5	57.0	57.0
HIV Status	POS	18	9	7	4	4	4	4
	NEG	4	2	1	1	1	1	1

Table 6.32

Description of Participants on capreomycin.

		T0	T1	T2	T3	T4	T5	T6
n		0	4	3	4	5	2	1
dropout			0	1	0	0	3	1
Gender	M	0	0	0	1	1	0	0
	F	0	4	3	3	4	2	1
Age (years)	Mean		32.1	32.0	38.0	35.0	36.7	35.4
	SD		7.8	8.3	2.2	7.2	2.0	
	Min		18.6	22.5	35.2	22.6	35.3	35.4
	Max		42.0	38.2	40.5	40.6	38.1	35.4
	Median		32.5	35.2	38.2	38.1	36.7	35.4
Weight (kg)	Mean		53.8	48.8	48.9	50.5	56.3	55.6
	SD		9.9	6.8	8.0	8.5		
	Min		52.8	58.0	43.7	41.9	56.3	55.6
	Max		72.4	58.0	58.1	59.4	56.3	55.6
	Median		54.0	58.0	44.8	50.4	56.3	55.6
HIV Status	POS		4	3	4	5	2	1
	NEG		0	0	0	0	0	0

Many participants were first time TB infections; they had not been previously treated for TB or DR-TB (Table 6.33).

Table 6.33

History of TB treatment

	HJH		SRH		Total	
	n	%	*n*	%	*n*	%
First Time Infection	5	56	8	62	13	59
Previously been Treated for TB	4	44	5	38	9	41
Switched to capreomycin rather than kanamycin	0	0	5	39	5	23

When looking at the participants that were most adherent to the study protocols (the six participants that completed the study), no distinct pattern was observed with age, education or marital status (Table 6.34).

Table 6.34

Age Education and Marital Status of Most Adherent Participants

Participant	Age (years at enrolment)	Education Level Completed	Marital Status
K004	21.2	Grade 10	Single
K005	32.4	Grade 12	Cohabiting
K007	18.6	Grade 11	Single
K008	29.4	Grade 10	Single
K009	30.1	Grade 10	Single
K010	35.1	Grade 10	Cohabiting

Majority of the participants had only completed a Grade 10 level of education. Furthermore, the majority were unemployed. Although the language of choice varied, the majority of the participants reported being most comfortable in English with regards to conduct study-related procedures (Figure 6.1).

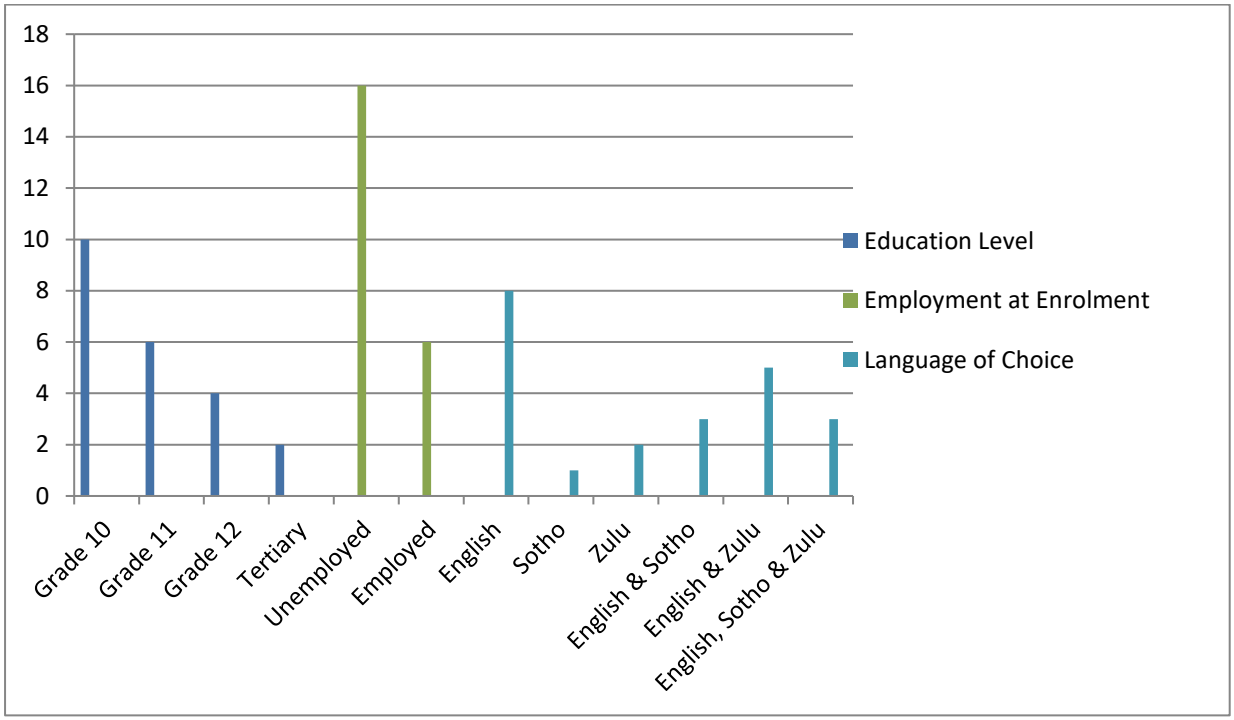

Figure 6.1. Education, employment, and language of participants enrolled

6.4.2. Blood Samples

The collection of blood samples for the pharmacokinetic measurements as well as creatinine measurement proved difficult for various reasons.

With regards to the pharmacokinetic measurements; this study started by analysing kanamycin only, and then moved onto capreomycin to increase the sample size.

Initially, the kanamycin pharmacokinetics in this study was the first to be measured in DR-TB patients in South Africa. Moreover, thus, a protocol needed to be developed. The established laboratories such as CLS, National Health Laboratory Service (NHLS) or other private laboratories could not perform these measurements, and so the pharmacokinetics and biochemists at SMU were responsible for this. Although they had the expertise and

equipment, the laboratory was over an hour drive away, and this resulted in some complications, such as haemolysis of the blood samples and spillage on the way to SMU despite the correct storage of these samples. These complications resulted in a significant amount of missing pharmacokinetic data.

Also, although creatinine was measured as per standard hospital care, the results were difficult to track on the NHLS website. When the study team searched the NHLS database (multiple times under numerous searches) results could not be accessed/found when searching for participants ID numbers, hospital numbers, names and so on. From observation, it appeared possible that the results may have been captured incorrectly, perhaps with incorrect digits with ID and hospital numbers, as well as incorrect spelling of participant names.

The complications of performing these pharmacokinetic measurements, including the transportation of samples have been established and need to be taken into consideration for a more extensive study.

6.4.3. Quality Assurance, including Record Keeping and Data Management

QA was an issue in this study and needs to be considered for more extensive studies. These issues with QA were portrayed mainly with the record keeping and data management.

Each participant had two files: a study file and a hospital file. At times, information was obtained from the hospital file for the study file. Also, various results were planned to be obtained from the hospital file for the study. However, much of this information was not in the hospital files, which made the obtaining of information for the study file extremely difficult. This included height and medical changes noted in the participants (physical and psychological).

Also, much of the results, specifically the sputum results as well the creatinine results were required from the NHLS. However, these results were often not placed in the hospital file. Subsequently, when searching the NHLS website, the results could not be found. This is possibly due to the incorrect capturing of the data. However, this impacted the study significantly as much of the information became missing, although the tests were carried out as per the protocol.

6.4.4. Medical Management, including Change in Protocols and Medications

Medical management of participants in this study took place as per the NDoH guidelines for patients with DR-TB. However, on observation, between sites, the management differed, which affected the uniformity of the study, but also made statistics and record keeping for National Guidelines difficult.

HJH is an outpatient facility while SRH is an inpatient facility (for the first few weeks of treatment). Availability of drugs also differs, as HJH only had kanamycin (and bedaquiline is some cases), while SRH had kanamycin and capreomycin. Therefore, patients at HJH were provided mostly with kanamycin, and only in some cases, the motivation for bedaquiline was possible; whereas, at SRH, capreomycin was readily available for those participants displaying adverse effects from kanamycin. As these participants were switched to capreomycin, it created a variance between the sites.

Furthermore, HJH had multiple counsellors as part of their team, whereas SRH did not. This could impact the compliance of patients. The audiology services available at SRH and HJH were also different, due to the inpatient and outpatient setup.

These differences in treatment complicate the feasibility of studies, mainly where sample sizes may be small, and so variations of treatment are difficult to analyse.

6.4.5. Resources

In general hospital settings, the limited resources with regards to personnel, equipment, and training were identified. This would impact the feasibility of future studies.

This current study compensated and planned for the lack of recourses, however, despite this, the impact was still felt.

As UHF PTA equipment and DPOAE equipment was not available in the hospital settings, the PTA audiometer was borrowed specifically for the purpose of the study for a limited period. Therefore, when the company required the borrowed equipment, further testing could not take place. Although testing was possible for this study, the equipment it is not freely available, which impacts further studies, as well as the general standard of care where UHF monitoring would be ideal.

Furthermore, the study coordinator was funded for a 12-month period to assist with this study, and thus after this period, there was no personnel available to assist with the day to day running of study procedures. As per the dropout rate initially calculated, one year was sufficient to collect the data. However, due to unforeseen dropout rates, the sample obtained was extremely small. The researcher was not able to draw blood samples as it is outside her scope of practice, and so this impacted the feasibility of this study, but would also impact the feasibility of future studies. Furthermore, in daily practice, there are not enough skilled personnel to assist with ototoxicity monitoring and possible pharmacokinetic measurements.

In summary, a pharmacokinetic study as such, requires audiological equipment, skilled personnel, various equipment, as well as support personnel for QA and transportation of blood samples. These aspects are expensive, and thus a larger budget is needed for a more extensive scale study.

6.4.6. The potential of whether TDM could potentially be utilised regarding dosage adjustments of kanamycin and capreomycin

This study aimed to measure these pharmacokinetic factors and to evaluate it according to the efficacy of treatment as well as ototoxicity. However, upon testing these pharmacokinetic factors, the mean peak level for kanamycin was 20 μg/ml (±16.5) and 8.1 μg/ml for capreomycin (±5.5).

The range of desired peak levels for capreomycin appears to be between 20 μg/ml and 40 μg/ml (Reisfeld et al., 2012) and between 20 μg/ml and 35 μg/ml (Mugabo et al., 2015). Although the mean peak from kanamycin was within the desired range, the SD was substantial, indicating many peak levels below this range.

Adjustment of these drugs would require, at times, to quintuple the dosages. This is a significant adjustment, with not enough evidence to support the need for this, as cultures often did covert, despite these low peak levels. Research supports that increased trough levels result in toxicities, specifically ototoxicity. The larger the dose, the likelihood of more significant trough levels, and thus toxicities (Mugabo et al., 2015; Pechere & Dugal, 1979). As many participants were outpatients, there was not enough medical monitoring of the participants to deal with problems or emergencies that may arise with dosage adjustments.

Therefore, from this study, the feasibility of conducting TDM in the treatment of DR-TB patients was not established. However, more extensive studies are recommended to explore this possibility further.

6.4.7. Summary of Feasibility Findings

In summary, of a potential 268 participants at both hospitals, only 22 were enrolled after 12 months of recruitment. This poor enrolment and retention were for a variety of

reasons; from a willingness to participate in exclusion based on the study inclusion and exclusion criteria.

The peak levels of many kanamycin patients were sub-therapeutic, even though the mean peak was 20 μg/ml (±16.5), while the peak levels of capreomycin were all sub-therapeutic with a mean of 8.1 μg/ml (±5.5). Trough levels for both kanamycin and capreomycin were below 10 μg/ml, which would indicate non-toxic levels.

However, despite these pharmacokinetic results, changes in hearing was noted (more so for kanamycin than capreomycin), as well as reduced CrCl levels with the kanamycin patients. Therefore, toxicity was noted. Lastly, despite the sub-therapeutic peak levels, patients culture converted within the first two months of treatment.

Therefore, with the small sample size achieved, as well as erratic levels with regards to the pharmacokinetics, substantial issues with regards to the feasibility of larger studies were identified. These issues, such as willingness to participate, blood sampling issues, large variations with results, QA, as well protocol variations between institutions need consideration in order to conduct a larger and necessary study.

Chapter 7: Discussion

In this chapter, the results as presented in chapter 6, will be discussed in relation to the literature and probable explanations where possible. As above, the audiological and pharmacological results will be discussed in the relevant sections, concluding with feasibility aspects of this study.

7.1. Audiological Results

The audiological results address the aim of determining the changes in hearing levels in patients treated with kanamycin and capreomycin for DR-TB, by looking at the prevalence of abnormal findings on baseline assessments and determining the change in hearing levels from baseline.

7.1.1. Pure Tone Audiometry and Distortion Product Otoacoustic Emissions

When examining the audiological results (PTA and DPOAEs), a definite pattern was observed, indicating the ultra-high frequencies (9kHz to 16 kHz) being affected first, followed by some high frequencies (specifically 6 kHz and 8 kHz).

An aim of this current study included the identification of changes in hearing from baseline measures. The mean results at the relevant weeks were explicitly presented in chapter 6 where the loss in the high frequencies (8 kHz and below) was seen from week 6, with UHFs being affected from week 4. The right ear showed a significant change from week six to 6 kHz, and week ten at 8 kHz, yet from week four at 11.2 kHz and above. The left ear showed mean significant change from week eight at 6 kHz and 8 kHz, yet from week four at 16 kHz. With the DPOAEs, a mean loss of 6 dB or higher was seen by week two in the right

ears at 6 kHz and 8 kHz, yet only from week 8 in the left ear. From week 2, a significant change of 10 dB or greater (with PTA) identified 23 ears (77%). This was at one or more of the ultra-high frequencies. Slightly less change was noted with the DPOAE ultra-high frequencies whereby week two, half the participants showed a deterioration of 6 dB or greater. However, the ultra-high frequencies with DPOAEs only tested up to 10 kHz, where the PTA tested up to 16 kHz. Furthermore, at baseline, half the participants displayed some sort of hearing loss, as measured with PTA. This ranged from a 30 dBHL threshold at one frequency to a 40 dBHL threshold at four frequencies bilaterally.

As cochleotoxicity research supports the damage initially occurring to the other hair cells at the basal end of the cochlea, the higher frequencies are initially affected (Peterson & Rogers, 2015). From this research, as well as from the limitation of the audiometer, we can assume the hearing loss is greater than recorded as depicted below at 16 kHz.

The findings of the current study support the literature regarding the general nature and configuration of an aminoglycoside /polypeptide induced hearing loss (Harris & Heinze, 2015) in the DR-TB population (Harris et al., 2012). In both ears, the greatest change in hearing levels is noticed in the ultra-high frequencies (9 kHz to 16 kHz). The greatest change in hearing was at 11.2 kHz bilaterally. As with ototoxicity, the outer hair cells are affected first, indicating the higher frequencies being affected by the lower frequencies (Peterson & Rogers, 2015). This was evident in the current study, where, the UHF and HF were affected.

Many studies investigating ototoxicity in the TB population only studied ototoxicity up to 8 kHz, and the loss in the UHFs was not necessarily monitored (Sharma et al., 2016; Ghafari et al., 2015; Javadi et al., 2011). Sharma et al. (2016) identified high-frequency hearing loss, of 12% after week 6. Likewise, this current study showed mean high frequencies being affected from week 6. The high-frequency hearing loss has further been identified in other populations being treated with aminoglycosides (Black et al., 1976; Fausti

et al., 1993), yet UHF testing showed the increased sensitivity of identifying ototoxicity. This was observed where UHF identified 95% of ears in comparison to 67% with general high frequencies (Fausti et al., 1993), as well as another study identifying 82% of ears with change when monitoring up to 20 kHz (Fausti et al., 1992). This current study identified a significant change in 77% of ears with UHF PTA at week 2, where general high frequencies did not detect any change at this week.

However, in contrast, Duggal and Sarkar (2007) discuss that in their sample of MDR-TB patients, 18.75% of the patients developed sensorineural hearing loss involving higher frequencies (4 kHz to 8 kHz) while only 6.25% also had involvement of speech frequencies (0.5 kHz to 3 kHz). This could imply the limited relevance of testing the high frequencies, and specifically the UHF. However, according to the review by Moore, Stone, Fullgrabe, Glasberg & Puria, (2008), a benefit for speech intelligibility is observed in the higher frequencies, specifically in a noisy environment. Therefore, identifying loss in the UHF, before it moves into the high frequencies is beneficial to reduce difficulty with speech discrimination possibly.

Presence of the hearing loss at baseline could be a result of various factors. However, no specific cause was reported by any of the participants. The hearing loss could potentially have been caused by previous use of aminoglycosides, other illnesses that were not reported, noise exposure, HIV and/or poor nutrition (Wang et al., 1999; Bisht & Bist., 2011; Schellack & Naude, 2013; Khoza, 2010; Hoffman, et al., 1987).

In summary, this current study identified significant UHF loss of hearing and cochlear function as measured with PTA and DPOAEs. The UHF loss was noted before the high-frequency loss, which in this current study was at 6 kHz and 8 kHz with PTA and from 2 kHz with DPOAEs. However, PTA is not routinely performed at above 8 kHz when monitoring ototoxicity. PTA normative values for frequencies above 8 kHz are not yet established clearly

(de Sá et al., 2007). However, these UHF are still useful for audiological monitoring of ototoxicity. By detecting a change in frequencies above 8 kHz, ototoxicity can be identified before it involves speech frequencies and affects communication (Singh, Saxena & Varshney, 2008). The need for standardised measures to monitor and grade this loss is essential to fully understand the extent and pattern of this ototoxicity, specifically in the DR-TB population.

7.1.2. Comparison of Pure Tone Audiometry and DPOAEs

The current study utilised both PTA and DPOAEs as a method of identifying and monitoring ototoxicity resulting from kanamycin and capreomycin. DPOAEs were chosen to compliment the PTA as they can detect minor changes in cochlear function prior to changes in hearing thresholds on either the conventional audiogram or UHF audiometry (Guthrie, 2008).

Some association of these PTA and DPOAE measures was observed in this current study. They both identified the right ears showing greater loss of hearing and cochlear function than the left ears. However, PTA did not identify a significant loss of hearing at 2 kHz, where, the DPOAEs did. This is in accordance with the literature, where DPOAEs are more sensitive than PTA (Guthrie, 2008).

This association, however, was not evident through the study; the PTA showed the greatest shift at 11.2 kHz, where the DPOAEs showed the greatest shift at 10 kHz. This does not correlate entirely, however, 11.2 kHz was not measured with DPOAEs, making a definite conclusion difficult. In the left ear, 4 kHz was the frequency most affected in the DPOAEs, which does not correlate to the 11.2 kHz in the PTA.

Despite these discrepancies in association in this current study, a positive relationship has been shown in various other studies. A positive correlation was shown between UHF PTA and conventional DPOAEs (up to 8 kHz) (Yu et al., 2014) with general PTA and DPOAEs (between 2 kHz and 6 kHz) (Campos & Carvallo, 2011) when monitoring

ototoxicity. Yet, there was no evidence of a robust relationship between DPOAEs and PTA in the industrial setting (Wooles et al., 2015). These discrepancies in the current study could be a result of a small sample size, as well as some missing data due to poor signal to noise ratios.

DPOAEs have however been useful in detecting early ototoxicity, where DPOAEs detected more ototoxicity earlier than with PTA. DPOAEs detected 70% of the ototoxicity by day 28, with PTA only detecting 22% at this time (Daud et al., 2014). In the current study, conflicting results are observed; the UHF PTA detected more ototoxicity by week 2 compared to the DPOAEs, yet DPOAEs detected ototoxicity at lower frequencies than the general PTA. The sensitivity of OAEs was seen by Hotz et al. (1994); when using TEOAEs, 90% of participants on amikacin were identified as showing ototoxicity (Hotz et al., 1994), where PTA found 7% of ototoxicity on a larger sample of patients on gentamicin and amikacin (Lerner & Matz, 1979). This was TEOAEs and not DPOAEs as with this current study.

In conclusion, this current study showed advantages when making use of DPOAEs to monitor ototoxicity in patients with DR-TB, as it allowed for early identification at 2 kHz. However, it is unclear if this would translate into behavioural changes and correlate to PTA at a later stage of treatment.

The investigation of the potential to use DPOAES to monitor ototoxicity in isolation, is relevant, specifically in South Africa where the prevalence of DR-TB is high, and the availability of audiologists and equipment, especially in rural areas may be low.

7.1.3. Symmetry of Hearing Loss

For this current study, asymmetry was considered as a 10 dBHL difference for PTA (Konrad-Martin et al., 2005) and 6 dB for DPOAEs (Roede et al., 1993) between ears.

The findings of the current study indicate that this difference between the right and left ears were noted with PTA in the UHF; 12.5 kHz and 14 kHz (noted on weeks 8 and 12)

and 16 kHz (noted on week 2). Asymmetry was further noted in different frequencies with DPOAES; at 4 kHz (on baseline, weeks 2 and 12), 10 kHz (on week 2) and 12 kHz (on week 10). Additionally, 36% of the participants reported difficulty localising at baseline.

Yet, hearing loss resulting from aminoglycosides is usually bilateral and symmetrical (Harris & Heinze, 2015). Furthermore, Black et al. (1976) showed a high-frequency loss with amikacin that was usually bilateral, and a study in Namibia on MDR-TB with kanamycin and amikacin showed that most of the hearing loss was also bilateral (83%) (Sagwa et al., 2015). Although the hearing loss was bilateral, symmetry was not discussed in this study. Yet, an audiogram provided in the article depicted symmetry (Sagwa et al. 2015).

Though a right ear advantage has been found in various studies, where the right ear generally displays less damage of cochlear functioning when measured with OAEs (Chung et al., 1983; Khalfa et al., 1997; McFadden, 1993). This could potentially describe some asymmetry; however, these differences are usually small of 2-4 dB (McFadden, 1993). This right ear advantage was further seen in male adults between 2-6 kHz, with differences of 1.5 to 2.5 dB between ears (Chung et al., 1983). However, these ‘asymmetries’ are minimal and not as much as 6 dB as found in the DPOAEs in the current study, and also the mean of the right ears showed a greater loss than the left ears.

This phenomenon of a difference between ears was noticed further at 4 kHz to 8 kHz where the left ear was more affected from cisplatin than the right ear (Schmidt et al., 2008), which shows that contrary to other literature, the cisplatin-induced hearing loss is not necessarily symmetrical. Huzing and de Groot (1987) also mention that aminoglycoside-induced hearing loss is not necessarily symmetrical, however, does not describe clear reasoning. Unilateral hearing loss, indicating asymmetry, was reported in patients taking amikacin where the bilateral hearing loss was noted in 18 patients, and unilateral loss in 11 patients (Javadi et al., 2011). Also, Sharma et al. (2016) described bilateral hearing loss in 13

patients and unilateral in five patients at week 6 of treatment of 100 patients (Sharma et al., 2016). In this current study, asymmetry was not explicitly noted at week 6.

As eight participants in the current study reportedly struggled with localisation at baseline, the overall baseline PTA results were examined. This was initially thought to assist in explaining the asymmetry that developed later. Yet, at baseline, half the participants displayed some sort of hearing loss, as measured with PTA. This ranged from a 30 dB HL threshold at one frequency to a 40 dB threshold at four frequencies bilaterally.

This reduced PTA at baseline could potentially explain the localisation difficulties reported, even in instances with no asymmetry. Localisation difficulties are present in people with hearing impairment (Brungart, Cohen, Zion & Romigh, 2017). More participants in this current study had some hearing loss at baseline than localisation difficulties reported. In some instances, localisation difficulties can also be present in individuals with normal hearing, explained by potential issues with auditory processing (Shamma, 2011). Hence, alternatively, these localisation issues could result from potential issues with auditory processing. As this is a very complicated auditory function (Shamma, 2011), these issues are not understood entirely.

The localisation difficulties could not directly be linked to asymmetry. It could bring a potential explanation in some cases, however, is not definitive and cannot be generalised to the entire group. There is thus no clear explanation for the asymmetry noticed, in that the right ear displayed a more significant hearing loss than the left ear. The explanations above do not account for the substantial differences noted at some frequencies. Pharmacologically, the drug does not enter one ear more than the other. Therefore, we may hypothesise that the asymmetry in hearing loss is likely a result of previous trauma to the ears or other such hearing loss. Conversely, the localisation complications, however, could potentially be identified by a loss of hearing at baseline or auditory processing issues. Furthermore, the

previously understood configuration for a symmetrical hearing loss resulting from aminoglycosides may need to be redefined and understood.

7.1.4. Percentage and Overall Change in Hearing/Cochlear Function

This study aimed to look at the prevalence of abnormal findings at baseline assessments and determine the change in hearing levels from baseline. At baseline, half the participants (50%) displayed some hearing loss as measured with PTA (ranging from a 30 dB threshold at one frequency to a 40 dB threshold at four frequencies bilaterally). From the results of the 15 that were present for more than the baseline; all showed ototoxicity in DPOAEs, 93% showed ototoxicity with TUNE and ASHA, and 7% with CTCAE. These scales (CTCAE and TUNE), as well as the ASHA system, only, looked at PTA. Although the sample was small, it does portray the variation of percentage of hearing loss based on the different grading scales used; depicting the need for a standardised description of ototoxicity in this population.

This percentage calculation did not separate those on kanamycin and capreomycin, as many started on kanamycin and switched to capreomycin, which made it difficult to describe. Thus, depending on which frequency range that was used to describe the hearing loss, between 7% and 93% of participants experienced a significant loss of hearing. However, only 7% experienced this at 8 kHz or below.

This range identified in the current study is seen across various other studies, depending on the classification method. In other research, the incidence of cochlear damage due to aminoglycosides ranges from 7–90% (Petersen & Rogers, 2015). An MDR-TB study with amikacin, using the ASHA criteria (up to 8 kHz), found 70% experienced ototoxicity (Javadi et al., 2011). Another MDR-TB study using the WHO guidelines (Lin et al., 2011) identified approximately 23% with hearing and vestibular issues post-treatment (Jacob &

Ross, 2012). Ramma and Ibekwe (2012) identified 47% of patients with MDR-TB and XDR-TB with ototoxicity.

Other studies using aminoglycosides and capreomycin, not specifically with DR-TB show variable results. Ototoxicity from kanamycin in premature children was not statistically significant (Savidson et al., 1980), and kanamycin used in guinea pigs showed ototoxicity (Waterstrom, 1986). Subclinical loss from capreomycin was found 11% of healthy individuals (Akorn, Inc. Package Insert, 2015), which has been defined as a pure-tone average hearing loss of >25 dB at high (4 kHz) and low (1 kHz) frequencies (Nakajima, Kanda, Hosobuchi & Suwa, 2014). The definition of subclinical however is not found in the package insert. Furthermore, other aminoglycosides, not specifically kanamycin, showed 21% in cystic fibrosis patients with short-term treatment (Al-Malky et al., 2011).

This variability could be due to a potential of under-reporting, as well as the lack of clear guidelines for monitoring ototoxicity (Edson & Terrell, 1991; Petersen & Rogers, 2015). These grading scales, although detected some hearing loss, have broad criteria, and do not provide any recommendations based on the grades. These grades were also not developed in the DR-TB population, but mainly on the cancer population.

As per the previous sections, the definite presence of hearing loss was identified in this study, yet the criteria to grade the loss, and classify the percentage was complicated and varied. Therefore, although there is a correlation to other studies, the direct comparison is difficult to the variability in testing hearing and describing hearing loss.

7.1.5. Week of Greatest Change in Hearing Levels

In the current study, the greatest changes with DPOAEs from the previous study visit presented at week 2 for 2, 8, 10 and 12 kHz. The greatest changes with PTA from the previous study visit was week 2 (11.2 kHz, 12 kHz, and 14 kHz) and week 6 (6 kHz, 8 kHz

and 10 kHz). The least DPOAE changes were noted at weeks 6 and 10, and the least PTA changes were noted at weeks 4 and 8.

When describing the correlation between the DPOAEs and PTA in this study, it was concluded that although there were positive correlations between the two measures, there were various instances where the correlation was not noted. This discrepancy here, identifying the weeks of greatest change, is another instance of no correlation. The exact correlation of the DPOAE changes, in translating to the PTA as functional changes at a later stage are not known, however, should also not be disregarded. As per the conclusion in 7.1.2, the potential for the use of DPOAEs alone to monitor ototoxicity, without the use of PTA, needs to be further investigated in different situations and larger samples before recommending it to be used in isolation.

The most significant audiology results observed was in week 2 and week 6. Moreover, for outpatient treatment, specifically at HJH, the patients visit the doctor at baseline, week 2, and subsequently every four weeks, so at weeks 6, 10, 14 and so on (Gajee et al., 2016). This can translate into practical ways to monitor ototoxicity when devising a protocol to monitor DR-TB patients. As PTA is generally used to grade hearing loss and as well as to direct the change of dosage and treatment adjustments, PTA greatest changes will mainly be utilised. Therefore, in the first three months of monitoring, it is recommended that baseline testing, as well as week 2 and week 6 be conducted. As week 4 and 8 showed the least change, then the following test could be conducted at week 10 or 12.

Also, as patient dropout is exceptionally high, as seen in the current study, as well as from Gajee et al. (2016), combining audiological and medical visits are more beneficial, to ensure the patient only needs to visit the clinic once for both medical and audiological visits combined. This combination of audiological and medical visits would allow for immediate changes in treatment regimen by the doctor when ototoxicity is identified. This monthly

testing is recommended for a low resource setting, despite that two-weekly testing would be ideal in a setting with more resources and patient participation.

7.1.6. Differences in hearing for participants being treated with kanamycin and capreomycin

In this study, it was difficult to ascertain whether kanamycin or capreomycin was more ototoxic, as often, the participants that were experiencing ototoxicity were switched to capreomycin. Also, the sample size was small. Therefore, it is possible that these patients that were switched to capreomycin were more susceptible to ototoxicity, and the hearing loss cannot be attributed to the toxicity of the drug, but possibly to other factors such as genetic susceptibility, previous use of aminoglycosides, and other risk factors. Yet, when looking at weeks 10 and 12, those on kanamycin showed greater ototoxicity to those on capreomycin. These results are potentially skewed due to the switch to capreomycin and possible susceptibility of these patients to develop hearing loss.

When compared to other studies, the incidence of cochlear damage due to aminoglycosides, such as kanamycin, varies from 7–90% (Petersen & Rogers, 2015) as seen from the above studies. However, very little information is available on capreomycin alone; despite the 11% subclinical loss in healthy individuals (Akorn, Inc. Package Insert, 2015). The exact difference in ototoxicity, within the DR-TB, is therefore not exactly understood.

As capreomycin is more expensive, it is rarely used. Thus, the investigation of ototoxicity caused by capreomycin is difficult. Further investigation is imperative, as should the toxicity profile differ greatly, the expense of the medication could outweigh the expenses of post-kanamycin management.

7.1.7. Summary

In conclusion, hearing loss was noted in the UHFs first, prior to the high frequencies, as well and the correlation was not always noted between PTA and DPOAEs. Furthermore, the greatest weeks of change with PTA were at weeks 2 and 6. These factors have implications for ototoxicity monitoring.

In addition, symmetry, as previously understood for ototoxicity, was present in this study, as well as some other studies. This brings forth the need to revise the description of ototoxicity being bilateral and symmetrical, despite the pharmacological understandings of the mechanism.

It also highlighted the lack of ototoxicity grading scales, specifically relevant for DR-TB in the ultra-high frequencies. The already existing adult grading scales, namely the CTCAE and TUNE scales only grade up to 8 kHz and 12.5 kHz respectively. The ASHA system, although not a grading scale, identifies significant ototoxicity. However, the criteria are broad and do not provide different levels/grades of ototoxicity.

The potential for the use of DPOAEs to monitor ototoxicity alone, without the use of PTA, needs to be investigated further in different situations and larger samples before recommending them to be used in isolation without PTA. Lastly, the monitoring and description of ototoxicity specifically need to be standardised to obtain accurate and generalizable statistics.

7.2. Pharmacokinetic Findings of Kanamycin and Capreomycin

This section will discuss the results as presented in section 6.1., where the mean peak and trough levels are discussed for kanamycin and capreomycin, the results in relation to creatinine levels, and lastly the results in relation to culture conversion.

7.2.1. Investigation of the Mean Peak and Trough Levels for kanamycin and capreomycin: Pharmacokinetic Results

The results, which are described in further detail in section 6.2.1, depicted different dosages of kanamycin and capreomycin. Overall, the pharmacokinetic results obtained appeared erratic.

There are very few studies identifying the ideal pharmacokinetic levels of kanamycin and capreomycin, specifically in patients with DR-TB.

Reisfeld et al. (2012) identified an ideal peak range between 20 μg/ml to 40 μg/ml, and a trough of below 10 μg/ml with regards to capreomycin, yet this study was conducted on mice (Reisfeld et al., 2012). In this current study, the mean peak throughout the weeks was 8.1 μg/ml (SD ±5.5). This is significantly lower than the desired range, even with the SD considered; emphasising the possible non- therapeutic effects of capreomycin. The mean trough level was within the desired range with a mean of 0.7 μg/ml and thus did not reach toxic levels. Yet, in many instances, it was undetectable at 0.05 μg/ml.

In the kanamycin study by Mugabo et al. (2015), kanamycin was undetectable after 24 hours, showing possible insufficient dosing of kanamycin in the previous dosing. It is likely that this was the same in this current study. In this current study, this could perhaps be explained because, at times, the trough levels were taken after 24 hours after the previous dosing. As in-patients, it should have been approximately 24 hours, as the nurses did their

rounds at 10:00, yet as out-patients, it would depend as to when they reached the front of the line at the local clinic (if they went at all). It was the same as for the kanamycin trough levels when compared to capreomycin, as the mean was slightly higher at 1.3 μg/ml, yet it was also undetectable in many instances. Again, in some cases it may have been at more than 24 hours, but not in all cases.

Desired peak levels for kanamycin appear to be between 20 μg/ml and 35 μg/ml (Mugabo et al., 2015). In the current study, the mean kanamycin peak levels were higher than the capreomycin peak levels, at a mean of 20 μg/ml, yet with a large SD of ±16.5. Although at times kanamycin dosing reached the therapeutic range, the results were erratic and fluctuated considerably.

The lower peak levels would indicate that the drug is not reaching therapeutic levels and likely not 'curing' the DR-TB. Yet, in the study in Iran, 52.2% had peak levels below the therapeutic level, yet 89% responded to treatment successfully (Namazi et al., 2016). In this current DR-TB study, perhaps other drugs are assisting in the treatment in combination with the low peak levels. Although patients may culture convert, they are not followed generally for years after treatment, and thus they could relapse.

Generally, the elimination of aminoglycosides is significantly affected by impaired renal function (Pechere & Dugal, 1979). The treating doctors, particularly at SRH, withdrew the participants from the study drug when they were showing renal problems (n = 3). This was only seen in the patients taking capreomycin. Therefore, the elimination would not have been affected in this study at SRH due to renal issues, as participants withdrew. Pechere and Dugal (1979) further discuss how other pathological states, such as anaemia, fever, hypoxemia, major burns and so on, can affect the desired pharmacokinetic levels of aminoglycosides. All these patients in this study had DR-TB, which perhaps could have affected these low peak levels.

The kanamycin study had slightly different levels of HIV positive and HIV negative patients (Mugabo et al., 2015). In this current study, due to the small sample size, the HIV positive and negative patients were not analysed separately as initially planned.

The mean dose per kilogram for kanamycin was 14.6 mg/kg and for capreomycin was 15.2 mg/kg. According to the WHO (2014), a dose of 15 mg/kg is suggested for kanamycin and capreomycin once daily (5 – 7 days per week). Both the doses for kanamycin and capreomycin were thus on the target, yet the peak levels were still below the therapeutic range.

The mean half-lives for kanamycin and capreomycin were 9.3 hours (SD ±5.1) and 7.2 hours (SD ±1.4) respectively. Moreover, the volume of distribution (ℓ/kg) was for kanamycin and capreomycin was 2.5 (SD± 2.1) and 3.3 (SD ±2) respectively. In a study on healthy participants, the half-life was 3.2 (SD ±1) hours for kanamycin, and the apparent volume of distribution (ℓ) for kanamycin was 30.4 (SD ±9.8) (Park et al., 2015). In another study on MDR-TB patients (Mugabo et al., 2015) using kanamycin, the volume of distribution was 38.62 in HIV negative patients and 50.18 in HIV positive patients, as the absorption has been shown to be different in HIV positive and HIV negative patients. These figures on both HIV positive and HIV negative patients are a lot closer to the figure by Park et al. (2015) of 30.4 and significantly higher than the volume of distribution in this current study of 2.5 for kanamycin. While the volume of distribution of significantly smaller in this study, the half-lives were significantly larger than expected, as it was compared to 3.2 in healthy participants (Park et al., 2015) and 1.67 in MDR-TB HIV negative patients and 1.29 in MDR-TB HIV positive patients (elimination half-life) and 4.45 in MDR-TB HIV negative patients and 4.62 in MDR-TB HIV positive patients (absorption half-life) (Mugabo et al., 2015).

Furthermore, despite the ideal peak and trough levels, diagnosis can impact on pharmacokinetics, as seen with the pharmacokinetics of amikacin, where the patients in ICU with different diagnoses displayed different values with the volume of distributions. This highlights the fact that the clinical diagnosis can also impact the pharmacokinetics (de Gatta et al., 1996). Thus, patients with DR-TB may be displaying different kinetics to those with other infections. This highlights the importance for individualisation of treatment. These studies provide evidence for the possible positive effects of optimising dosage regimens of aminoglycosides. However, this study displayed erratic levels with considerable differences among individuals, indicating the need for a further study with a larger sample size to fully understand the pharmacokinetics in this population.

7.2.2. The relationship between the kanamycin and capreomycin kinetics with creatinine levels

The CrCl results, indicated that for participants taking kanamycin, the average creatinine clearance was reduced, yet the drug was still cleared through the system, as seen with trough levels below 10 μg/ml, while for participants taking capreomycin, much of the creatinine clearance was within the normal range (80 – 130 ml/min).

Due to the almost exclusive excretion from the body by glomerular filtration, the elimination rate of aminoglycoside antibiotics is affected significantly by an impairment of renal function (Pechere & Dugal, 1979). The predictive potential of nomograms can be significantly improved by consideration of some physiological parameters such as sex, age, lean body mass, haematocrit and characterisation of disposition kinetics by multi-compartmental models. Anaemia, fever, hypoxemia and significant burns are other pathological states which notably influence the pharmacokinetics of aminoglycosides (Pechere & Dugal, 1979).

Those participants taking kanamycin showed greater renal impairment than those taking capreomycin. This is consistent with the study by de Jager and van Altena (2002) where a high percentage of patients taking kanamycin showed renal impairment. In contrast, minimal renal impairment was noted in patients taking capreomycin (Aquinas & Citron, 1972).

However, in this current study, in those patients showing renal impairments, trough levels were still within a non-toxic range (below 10 μg/ml), even though mean peak levels were within the therapeutic range. Those with average creatinine clearance level (capreomycin), showed normal trough levels, yet reduced peak levels.

7.2.3. The Relationship between the Pharmacokinetics and Pharmacodynamics of kanamycin and capreomycin to Culture Conversion

Culture conversion for DR-TB is defined as two consecutive negative TB cultures (30 days apart) (Prasad, 2012). Culture conversion is this study was defined as one negative culture post-baseline- measurements. Although culture conversion is often referred to as two consecutive negative cultures, many cultures were missing from the various databases, and so for consistency between the participants, one negative culture was utilised. Furthermore, the study was conducted in the first three months of treatment, and so often another culture was not conducted.

According to the WHO and NDoH guidelines, although capreomycin and kanamycin are both used for DR-TB treatment; efficacy is not differentiated, only the toxicity profiles. Efficacy in this current study does not appear to be different in the beginning stages of treatment; despite the low peak levels. However, the long-term results were not obtained, and possibly participants reverted to positive cultures. However, the sub-therapeutic peak levels of kanamycin in some instances and capreomycin does not correlate to the negative cultures.

Yet, as per Namazi et al. (2016), despite the low peak levels being below the therapeutic range, 89% responded to treatment successfully. This could explain the low peak levels in this current study with the positive culture conversions.

Although, there is also the possibility reinfection at later stages, due to the Resuscitation-promoting factors (Rpf). Although this model is ill-defined in human infection, from the mouse models, Rpf support bacterial survival and reactivation of TB despite a culture conversion as these Rpf are invisible to the conventional culture (Mukamolova et al., 2017). Therefore, these low peak levels could indicate, that although patients may culture covert on the conventional testing methods, these proteins may still be present, and responsible for the reinfection at a later stage, and thus the low peak levels could, in fact, correlate to poor outcomes

7.2.4. Summary of Pharmacokinetic Findings

Overall, the pharmacokinetics of both kanamycin and capreomycin were not as expected. The peak levels of kanamycin (in some instances), and capreomycin were subtherapeutic, which does not correlate to literature. In accordance with the literature, capreomycin is not as toxic as kanamycin, and thus less nephrotoxicity in these patients was noted. In both the kanamycin and capreomycin, participants did culture convert, despite the low peak levels.

7.3. Pharmacokinetics of kanamycin and capreomycin in Relation to Hearing Levels

The findings of the current study indicate that the trough levels did not correlate to ototoxicity. In some instances, when looking at mean levels, dosage did correlate to

ototoxicity, yet when looking at individual patients, dosage often did not correlate to ototoxicity. This section will discuss these results in relation to the current literature.

7.3.1. The Relationship between Pharmacokinetics of kanamycin and capreomycin, including Dosing, with Hearing Levels

Ototoxicity of aminoglycosides is correlated with elevated trough concentrations and/or prolonged duration of exposure rather than with peak concentration (Droege et al., 2016). Yet, this was not observed in the current study, as trough levels for kanamycin were below 3 μg/ml at all times indicating no toxic levels, yet ototoxicity was observed at all weeks in different frequencies. With regards to PTA, at all weeks, ototoxicity was observed only above 8 kHz, showing that it did not yet affect speech frequencies: only the ultra-high frequency range. Yet, with DPOAEs for kanamycin, 2 kHz was affected (at four of the six-time points). However most changes were observed at 8 kHz and above. The capreomycin sample size was smaller, and often the trough levels were undetectable. These are participants that had initially started with kanamycin. The trough levels always remained below 2 μg/ml. Yet, with PTA, significant changes, at times extended to some speech frequencies, such as at 6 kHz at week 8 (T5). Majority of the changes were above 8 kHz, as with the changes observed with kanamycin. With DPOAEs in the capreomycin participants, the change was detected at all the frequencies in different weeks. These results do not correlate to this literature that elevated trough levels are associated with toxicity. However, the snall sample size could have influenced this.

In contrast, another study was done on amikacin used to treat MDR-TB. Peak and trough levels were not predictors in the classification of ototoxicity (Modongo et al., 2015). This is similar to the current study where trough levels were not related to ototoxicity. This study showed that cumulative AUC and duration of drug therapy is more of an indicator of

ototoxicity, rather than peak concentrations, as the ototoxicity increased sharply after six months of therapy (Modongo et al., 2015). However, as the current study on capreomycin and kanamycin only looked at ototoxicity up to three months, it is likely that the ototoxicity may still have appeared, despite the low trough levels. Recently, with the STREAM study, a protocol of nine months of treatment is introduced. The study is in phase 3, and final outcomes will likely be available in 2018 (RESIST TB, 2017). Yet, based on Modongo et al. (2015), it may not reduce ototoxicity.

A study conducted in the Netherlands looked at TDM of amikacin and kanamycin in patients with MDR-TB or XDR-TB (van Altena et al., 2017). Therapeutic drug monitoring from the beginning of treatment took place when necessary, and hearing tested from baseline (up to 8 kHz). The results of the audiometry showed a hearing loss in nine patients (11.3%), predominantly at higher frequencies (4 and 8 kHz). Cumulative dose, dose per kg bodyweight, duration, bodyweight, gender, age, and BMI did not correlate with the occurrence of ototoxicity. This may be explained by the fact that the dosage was guided by the C_{max} /MIC in individual patients since the C_{max} /MIC correlates to the efficacy of aminoglycosides (van Altena et al., 2017). Yet, this study only looked at frequencies up to 8 kHz, and cannot be compared to this current study, as audiometry tested up to 16 kHz. However, when looking at frequencies 8 kHz and below, only 7% of hearing loss was detected, without TDM. These two studies yield conflicting results.

7.3.2. Summary of Pharmacokinetics in Relation to Hearing Levels

The findings of the current study indicate that no correlation was observed with trough levels and ototoxicity. The dose per kg throughout the weeks for kanamycin remained stable and can thus not be correlated to the change in hearing. Further studies with larger

sample size and UHFA are needed to ascertain the exact relationship between pharmacokinetics and hearing levels.

7.4. Feasibility of the Study

Various factors impacted the feasibility of this study, but notably, participant factors, including a willingness to participate, enrolment and attrition, as well as data acquisition factors, such as issues with blood samples and quality assurance of the data.

7.4.1. Participant Factors: Respondent Enrolment, Willingness to Participate and Attrition.

Attrition and adherence were prominent themes in this current study, which impacted the feasibility. Attrition is often affected by adherence (Munro et al., 2007). In this current study, adherence to visiting the clinics for injectables, taking oral medication and returning for study visits was poor, with high dropout.

The sample was small; however, 62.5% of participants completed the study at Helen Joseph Hospital, when those that withdrew for medical reasons were not accounted for (five of eight participants). 20% completed the study at South Rand Hospital, when those that withdrew for medical reasons were not accounted for (one of five participants).

Adherence was an important concern with the decentralisation of treatment, which was also observed by Evans et al. (2017) showing that fewer than half the patients diagnosed in Johannesburg initiated appropriate treatment.

Gajee et al. (2016) also mentioned that missing at least one scheduled appointment at the RR-TB clinic (HJH) was strongly associated with poor treatment outcomes. Thus, it is likely that the poor adherence in this current study, which took place at the same site, affected the participants' overall treatment outcome. However, this data was unavailable.

It is postulated that the factors that contribute to poor adherence and willingness to participate are multifaceted.

Thus, each factor influences multiple others. Some of these aspects, however, include emotional factors, lapses in communication and educational level.

Emotional factors can affect the willingness to participate, as well as the adherence to participation. Furthermore, emotional facets can be influenced by counselling, communication and patient education (Awofeso, 2008; Das et al., 2014).

While this study has identified poor adherence factors and high attrition rate, there were several eligible patients who chose not to be a participant. It appeared that the diagnosis initially overwhelmed participants, especially with having to receive daily injections for months. The emotional aspect and idea of more needles and blood tests appeared to be too overwhelming. As the participants had nothing to gain directly from the study, willingness to participate was poor. Additional, inpatient influential factors affected willingness. Particularly at SRH, patients appeared to discuss the protocol among one another and 'convinced' each other of the negative impact of the studies. It was the view that they were utilised for tests to help other people and not themselves. One patient compared themselves in the study to 'lab rats'. This view was not observed at HJH, as participants did not necessarily interact with each other.

Adverse effects, including depression, likely affected the adherence. Morisky et al. (2008) further found adherence to medication can be affected by depression, lack of knowledge about hypertension, the complexity of the medication regimen, health care system perceptions by the patient, sexual dysfunction, side effects of medication, and reduced quality of life (Morisky et al., 2008). Although this study by Morisky et al. (2008) was not about TB, the majority of these factors are prevalent in patients with DR-TB. Many patients suffer from depression (Das et al., 2014) as well as the regimen is complicated. DR-TB medication side

effects can include gastrointestinal disturbances, psychiatric disorders, arthralgia, hepatitis, peripheral neuropathy, hypothyroidism, epileptic seizures, dermatological effects, ototoxicity and nephrotoxicity (Yang et al., 2017). Therefore, based on the hypertension study where adverse effects affected adherence, and the adverse events resulted from DR-TB, it is likely that these effects can influence adherence in the DR-TB population (Awofeso, 2008).

Due to the adverse effects of the DR-TB and medication regimen, coping skills are necessary. Morisky et al. (2008) found that knowledge of hypertension, patient satisfaction, and coping skills was significantly associated with medication adherence. With regards to patients with DR-TB; many receive counselling upon diagnosis. This immediate counselling may not be adequate and practical, due to the devastating aspects of the diagnosis and treatment regimen. Thus, the patients' capacity to understand the implications for treatment at the time of the education may be inadequate due to feeling completely overwhelmed. This could imply that education and counselling need to take place multiple times. Das et al. (2017) recommend regular monitoring of mental health status by trained counsellors.

Counselling is a critical aspect of DR-TB therapy (Das et al., 2014) as it can assist with coping skills, but also improves patient education, deals with stigma as well as social factors. The language of preference and skills of the counsellors also affect counselling and its ability to be effective. Counselling is vital for patient education (Awofeso, 2008). In Zambia, the significant factors leading to noncompliance for TB treatment included patients beginning to feel better, inadequate knowledge on the benefits of completing a course, running out of drugs at home and the TB drugs were too strong (Kaona et al., 2014). Furthermore, daily injections, pill burden, DOT, seasonal work, social problems, prior TB treatment, and adverse drugs effects were reported as major barriers to treatment adherence and retention-in-care by patients and providers (Shringarpure et al., 2016). With DR-TB drugs, many participants complained of vomiting from the drugs, as well as the painful

injections, likely reducing adherence. Counselling, regarding the explanation of the symptoms as well as outcomes of correct protocol compliance, could potentially improve adherence.

Furthermore, counselling will help address stigma and social practices. Shringarpure et al. (2016) identified three themes affecting adherence, namely: struggle with prolonged treatment, strive against stigma and toward support and divergent perceptions and practices. This study also reported the influence of traditional healers (Shringarpure et al., 2016). Many of these patients have poor socioeconomic backgrounds, are ill, are suffering from the stigma of TB and have a reduced quality of life (Kibrisli, Bez, Yuilmaz et al., 2015). Although this was not a study aim and was not recorded, various patients were noted to have received other medications from traditional healers. The study coordinator was not able to obtain much information regarding this topic, as patients did not want to share, but two patients mentioned visiting a healer. No other information was obtained; however, it is possible that this could also have affected retention and adherence, and perhaps the low pharmacokinetic levels. A psychosocial support program implemented for at risk of defaulting patients showed success in reducing default among MDR-TB patients (Kaliakbarova et al., 2013). Perhaps the implementation of this would be useful.

Social influences also affect patients' adherence. In two cases, the patients were keen to participate in the study, yet their husbands would not allow them to. Although it was up to the patient to consent, both these female patients appeared to have domineering husbands to whom they listened to. No reason was obtained as to why their husbands did not want them to take part. Again, the theme of counselling recurs, but in this case, counselling for the significant others also appears to be necessary.

Despite the positive effects of counselling, there are issues, including language barriers and proficiency of counselling. Specifically, in South Africa, language barriers must

be respected, due to there being 11 official languages. This study identified a variety of languages of preference. Two participants could only speak isiZulu, one could only speak SeSotho, and eight reported only being proficient in English. The remaining 11 participants spoke either: English and SeSotho, English and isiZulu or English, isiZulu and SeSotho. Thus, if the treating doctor was only proficient in English, the language barrier could have disrupted this communication with three participants; a significant number of the 22 participants. Communication can become hindered, and thus would affect education.

Also, the counsellors may not be as proficient in the TB regimen as the doctor, which may affect the education of the patient. Perhaps, the implementation of a more structured protocol of counselling would be beneficial. This structure protocol could be adapted from Morisky et al. (2008) where treatment-related attitude and behaviour problems that the patient may face for health care providers to provide reinforcement and advice. A scale as such may be a useful tool to assist in identifying those patients at risk of defaulting with their DR-TB medication and to assist in improving adherence.

Outpatients received counselling from counsellors at the clinic regarding the necessity of taking their medication. The inpatients received counselling from doctors administering the drugs, and sometimes from the nurses. However, no follow-up was done regarding the counsellors' efficacy. Sanchez-Padilla et al. (2014) found that poor treatment tolerance, a perception that treatment was inefficient, lack of information, incorrect perception of being cured, working factors and behavioural problems were factors related to treatment default. Many of these factors can be changed by correct and efficient counselling.

In addition to counselling by trained counsellors, family support has also shown to assist with compliance (Hutapea, 2009). Patients with TB showed increased levels of performance-avoidance and social avoidance than healthy control subjects (Kibrisli et al., 2015). Lastly, Hutapeas study (2009) showed that the more significant family support

indicated improved compliance. However, four of the most compliant participants were single, and two were cohabiting with partners. The married participants did not show the greater compliance. However, this study did not look at other family support such as parents and other significant family members.

Poverty is also a reality for many South African patients, possibly affecting adherence, and thus the feasibility of treatment and this current study. In a Uganda TB study, one of the findings for non-adherence was a lack of transport money to collect more drugs when they were finished as well as being busy at work (Amuha et al., 2009). From the current study, those few patients that were employed were hesitant to miss work for treatment. In a developing country where the unemployment rate is tremendous, losing a job due to illness is a scare for many. However, out of the six participants employed at enrolment, only one participant dropped out for work-related reasons, while another one of these did complete the study. Perhaps the combination of this family support structure assisted with his participation. The remaining four either were transferred elsewhere for treatment such as Sizwe Hospital, returned to their homeland or withdrew for other medical reasons.

Moreover, increased education level and age have been shown to improve adherence (Hutapea, 2009). Though, both education level and age did not appear to be associated with adherence in this current study. Hutapea (2009) found that the higher the education, the greater the age and the more family support indicated better adherence to medication. In this current study, six of the 22 participants completed the full three-month study period. They were considered compliant with the study procedures, which indicated that they were compliant with their DR-TB medication regimen, as it was a condition of participation. When looking at education, the majority of the participants had completed grade 10 (n = 10), with the minority having some sort of tertiary education (n = 2). The most compliance participants (n = 6) had mostly completed grade 10 (n = 4) with only one participant having completed

grade 11 and one having completed grade 12. These results by Hutapea (2009) are thus in contrast to this current study, where education level did not seem to influence adherence. Also, the average age however in this study was 33.78 years, where the six most compliance participants were mostly below this age, with only one of these participants being 35.1 years. This current study does not support the notion that increased age, education and family support improves adherence. However, the sample was small to make a definite conclusion.

Although many of these factors, such as poverty, stigma and emotional difficulties were observed in the participants by the study coordinator at the study visits, and are necessary to consider, no single pattern could be observed. However, the sample was too small to find trends. The most significant trend that could be a smaller dropout from HJH compared to SRH. HJH had more trained counsellors, who spoke a variety of languages. This support and DR-TB education appear to have positively affected adherence and reduced attrition. As individual counselling may not always be feasible, possible support groups by a trained counsellor would assist in adherence.

7.4.1.1. HIV Status, ARVs, and DR-TB.

There is an increasing number of MDR-TB and XDR-TB cases in South Africa, which is likely representing an unrecognised and evolving epidemic rather than sporadic, localised outbreaks. The combination of a mostly affected HIV population provides an ideal condition for a DR-TB epidemic. HIV infection has shown to adversely affect the outcome of DR-TB treatment (Andrew et al., 2007). Someone who is infected with HIV and TB is more likely to become sick with active TB (WHO, 2013). Andrews et al. (2007) further mention that HIV clinics are sites are clustering of TB susceptible individuals, and, in the presence of unrecognised TB, they provide another favourable setting for the rapid spread of DR-TB.

The majority of participants in the current study had HIV co-infection and relative risk of TB among HIV-infected persons, compared with that among HIV-uninfected persons,

ranges from 20- and 37-fold, depending on the state of the HIV epidemic (Getahun et al., 2010). However, in South Africa, where HIV is rife, the risk of TB is as well. In 2015, there were an estimated 480 000 new cases MDR-TB cases worldwide and 100 000 RR-TB cases who were eligible for treatment, yet only 12 000 enrolled (20%), with the top six countries accounting for 60% of the new cases, one of which being South Africa (WHO, 2015). Also, with 33.2 million persons infected with HIV, one-third are also estimated to be infected with TB (Getahun et al., 2010).

Interestingly, another study showed the stepwise evolution of drug resistance, despite stringent treatment adherence, which is impacted by HIV. This study took place at a South African gold mine with a well-functioning TB control program (Calver et al., 2010). The findings suggested that existing TB control measures were inadequate to control the spread of drug-resistant TB in this HIV co-infected population. The data from this study call for improved infection control measures, implementation of rapid diagnostics, enhanced active screening strategies, as well as pharmacokinetic studies to determine optimal dosages and treatment regimens (Calver et al., 2010).

Although South Africa has one of the most extensive ARV programs internationally, only half of the HIV infected participants were on ARV therapy at enrolment, while the other half began treatment within the first month of TB treatment. Of the six participants that completed the full three months of the study protocol, five were HIV infected. Of the four total participants transferred to Sizwe Tropical Disease Hospital as they were sputum positive, one was HIV negative. Therefore 25% of the sputum positive participants were HIV negative. The outcomes of the HIV negative participants are unknown, as one wished to withdraw from the study, one was transferred to Sizwe Hospital, one completed the study and the last of the four returned to his hometown.

HIV infected patients are considered high risk for missing appointments in the treatment of DR-TB (Gajee et al., 2016). The feasibility was affected possibly by this sizeable HIV-DR-TB coinfection rate, as HIV patients are at higher risk of adherence to medication. This must be noted in further studies with a specific focus on retention of HIV patients.

7.4.1.2. Decentralisation of treatment.

The decentralisation of treatment identified many complications. Specifically, for this study, the decentralisation identified issues with participants returning for treatment, which impacted the feasibility of the study.

This was observed through the two sites at SRH and HJH; a variety of inpatient and outpatient treatment. HJH, SRH, and Charlotte Maxeke Johannesburg Academic Hospital are the three decentralised DR-TB hospitals in Gauteng (Evans et al., 2017). However, SRH it is also one of two Gauteng-based hospitals that treat DR-TB patients on both an out- and inpatient basis. (Gauteng Department of Health, n.d.) South Rand Hospitals' inpatient treatment period for DR-TB ranges from between two and eight weeks and they treated as outpatients. Helen Joseph Hospital, in contrast, treats patients as outpatients, whereby they visit their clinics daily and return to Helen Joseph hospital for follow-up visits at scheduled intervals (Gajee et al., 2016). Thus, for this study, nine participants received treatment at Helen Joseph Hospital and 13 at South Rand Hospital.

Decentralization of treatment, as discussed by the NDoH (2011) was necessary as the number of patients diagnosed with MDR-TB far exceeded the number of hospital beds in the centralised MDR-TB units. The waiting times and waiting lists also resulted in many infectious and untreated patients exposing family and community members to DR-TB bacilli (NDoH, 2011). They further described DR-TB as a human-made problem, primarily due to

human error in either management of drug supply, patient management, prescription of chemotherapy or patient adherence.

However, as per the data from this current study, 59% of this participant sample had never been treated with TB before, and the DR-TB was their first infection. Only 41% had been treated with TB before. Thus, due to these first time TB infections, it cannot be a direct result of errors in the prescription of chemotherapy, patient adherence, management of drug supply and patient management. It is probable that these newly infected TB patients were infected from others with DR-TB in the community who were still currently infectious.

This study also further identified various themes with the decentralisation model, as noted from informal interviews with the participants. The issues encompassed problems with visiting the clinics daily for injections, as participants complained of the painful nature of the injections with no recovery noted yet resulting in unpleasant side effects. Furthermore, the participants reported anxiety regarding the waiting times at the clinic, which impacted employment and job sustainability. The need to provide food for their families in conjunction with the stigma of visiting the clinic daily outweighed the desire to receive the injections. Many feared isolation and judgement based on their diagnosis.

Control of the spread of the disease, upon observation, was also identified as an issue with decentralisation. Participants received the in-depth counselling of DR-TB transmission and requirement to wear masks. However, this further enhanced the stigma and isolation. Participant reports also comprised of transportation issues when wearing a mask; they may not have been allowed in the taxi wearing a mask, for fear of infection of the others, and as a result, they did not wear the mask in the taxi. Many participants were only seen putting the mask on when they entered the hospital for follow-ups. Furthermore, Evans et al. (2017) showed that the median time from sputum collection to treatment initiation was 33 days. This

demonstrated how many patients remained infectious in various communities prior to treatment.

Many patients were extremely ill and too weak to visit the clinic for their injections. Due to poverty, access food was a prominent issue. Patients reported taking the oral medications on empty stomachs and subsequently vomiting. As many of the participants in this current study lived in informal settlements, consideration was given to the lack of adequate heating and ventilation. Medication adherence and infection control could not be examined conclusively as the participants were not followed when they were at home. Also, Bedell et al. (2000) showed 76% with discrepancies between what doctors prescribe and what patients take in actual practice. Although this study was not explicitly done on HIV/TB medication, it can be extrapolated to this population (Bedell et al., 2000).

A study in California reported high success cure rates of MDR-TB when treated as outpatients; however, those with underlying HIV had poor outcomes. They also reported no secondary cases (Burgos et al., 2004). Moyo et al. (2015) considered a community-based DR-TB program that was implemented in Khayelitsha. Loss to follow-up was high, and overall long-term survival was poor. This study, by Moyo et al. (2015) concluded by stating that further research is needed to support retention of DR-TB patients on treatment, even within the community-based treatment programs (Moyo et al., 2015). In South Africa, where HIV is rife, and living situations are complicated, secondary infection is a high possibility. Therefore, the success of inpatient versus outpatient treatment is not merely based on the hospitalisation factors, but many other variables that must be considered

The decentralisation model has some positive factors, although many shortfalls were noted. In this current study, as 59% were new TB infections, it is a clear indicator that infectious patients are spreading DR-TB to others, and the model of reducing the infection is not ideal.

Community-based treatment is not merely an alternative to centralised treatment, even though inpatient treatment is extremely costly (Sinavonic et al., 2015). When comparing this study to the current study conducted, only six participants continued throughout the three-month period which is a mere 27% of the sample. It is unsure whether they completed the remainder of their DR-TB therapy, however, based on their reasons for dropout from the study, it is likely that many did not complete their therapy. As some participants transferred to a centralised treatment program (Sizwe Tropical Disease Hospital), it is likely they continued treatment due to the inpatient regimen.

Padayatchi and Friedland (2008) suggest that patients with MDR-TB or XDR-TB could be admitted to institutions closer to their homes with subsequent discharge and home-based care. This could perhaps alleviate the transmission of the infection to others as they would be hospitalised in the infectious stage. However, infection control within DR-TB hospitals within South Africa has been shown to be poor, which is also a concern of inpatient treatment, whether long or short term (Farley et al., 2012). Thus, we can see, from this sample, that loss to follow up was high. Moreover, based on this, it is hypothesised that the outcomes were poor.

In summary, the treatment factors affecting the outcomes for DR-TB treatment are complex. On the one hand, long-term inpatient care is ideal, as it prevents transmission to uninfected counterparts. However, this results in further social and emotional issues.

Therefore, centralisation or decentralisation is not the only factor to be considered; instead counselling education, support and individualised treatment programs depending on each patients' needs. This, however, is difficult in a low resource setting. Yet, this decentralisation did significantly affect the feasibility outcome of this study and must be considered for further research.

7.4.2. Blood Sampling, Quality Assurance and Medical Management

Various other aspects affected the feasibility of the study. This included difficulties with the blood sampling, as well as various quality assurance hurdles, that must be considered for a future study. However, this depicts a real-life situation in South Africa, where DR-TB patients receive treatment as outpatients, and so they had to wait for hours to between the peak and trough levels.

Due to the limited resources in South Africa and capability of the laboratories, the pharmacokinetic measurements needed to transpire at SMU; over an hour's drive. Due to this, haemolysis of the samples occurred as well as spillage. Occasionally, blood was also not drawn due to participants' wishes. Thus, in many cases, part of the pharmacokinetic results was missing a total of 30 times, where only 51 samples were analysed fully. At times, the trough levels were obtained for some of the 30 samples. However, the peak levels were often missing. All efforts were taken to transport the samples correctly, according to GCP guidelines, yet as expected various difficulties still occurred. This highlights the need for more laboratories to perform these complicated measures. With the provision of services, correct transportation must also be ensured. Furthermore, many creatinine levels were not obtained. The creatinine results were planned to be obtained from the NHLS. However, much was accessed after the study. Upon searching for the creatinine levels on the NHLS database, many results were missing. The samples were drawn from the patient as noted by the study coordinator. The reason for missing results are unknown, but it could be a result of incorrect data capturing. Overall, the laboratory system within South Africa needs to be strengthened to provide efficient, cost-effective and reliable services to the large population that requires these tests. With a stronger national health laboratory system, the feasibility of research within this population will also be increased.

Also, as the medical management differs slightly between sites, national health statistics become compromised. As the protocol was slightly different between HJH and SRH, as discussed in Chapter 5, there was variability in results, and subsequently, the feasibility of the original study was affected.

7.4.3. Summary of Feasibility of Performing TDM on DR-TB Patients on kanamycin and capreomycin

Many aspects were identified that affected the feasibility this study, which affected the validity of generalisation of the results to a larger scale. Participant enrolment, willingness and attrition were a prominent factor, and various reasons were hypothesised.

The central theme that may be able to assist this is more in-depth counselling and emotional support for participants. Also, it is imperative to ensure that another study does not rely on the data capturing of the NHLS as data can become lost, impacting the overall outcomes of the study. Furthermore, as the pharmacokinetics method is clearly established, better quality control can be put in to place for a more extensive study with regards to blood sampling.

In summary, based on the audiological and pharmacokinetic results, TDM would not be feasible at present based on the limited data. More conclusive data and more prominent studies need to be conducted to further establish the pharmacokinetics of kanamycin and capreomycin in relation to toxicity and efficacy in patients with DR-TB.

Chapter 8: Ototoxicity Mobile Application

Hearing loss and pharmacokinetics factors have been described, with the existing monitoring protocols. From Chapters 4, 6 and 7, it was evident that there is no clear-cut definition and protocol for monitoring ototoxicity as well as a description of a significant hearing loss suitable to be used in this specific DR-TB population. Therefore, this chapter recommends a standard ototoxicity monitoring protocol with a defined grading system relevant in the South African DR-TB context. It further discusses the development of a mobile application that was created through this research study.

8.1. Rationale for the development of an ototoxicity monitoring protocol and grading system for the DR-TB population and considerations for the South African context

In South Africa, there is currently no set protocol for monitoring ototoxicity in the TB population. A study by Khoza-Shangase and Stirk (2016), showed that some hospitals that included have since implemented their own programs, yet there was no clear standard for managing the detected ototoxicity. The establishment of a monitoring program with an intervention method is needed.

However, various cultural, social and context-specific considerations need to be considered. These considerations include the acknowledgement of patients defaulting on their treatment, the influence of African Traditional Healers on many patients, the 11 official languages that can contribute to communication difficulties, as well as the limited number of

audiologists available in South Africa to implement and manage an ototoxicity monitoring protocol.

There are other factors for consideration which are specific to this DR-TB population. Defaulting from treatment and dropout rate was a dominant theme in this current study. Various issues have been identified in other studies as well. These reasons ranged from economic issues and poor tolerance and response to treatment. Economic issues included a return to work and complex social situations. Other reasons for default included behavioural problems (mainly substance abuse) (Sanchez-Padilla et al., 2014; Dooley et al., 2011), lack of belief in treatment, side effects and feeling healthy (Sanchez-Padilla et al., 2014). Dooley et al. (2011) further found that hospitalisation and positive sputum after three months of treatment was a risk of default.

These issues are important to identify and incorporate into a monitoring program. As identified in this study, among employed patients, their jobs were a priority over treatment and audiological monitoring. Also, many patients were living in poverty, and so essential human needs were not always met, such as food, shelter and hygiene. Thus, expecting these patients to return for DR-TB treatment and monitoring may not be feasible until their basic needs are met. This is an aspect to consider when counselling the patient, and in-patient treatment may need motivation for in some cases. Also, referral to a social worker to assist with grant applications may be necessary. Interdisciplinary communication would be necessary as well to communicate with employers to explain the necessity of attending hospital visits, as well as the legal implications of not allowing patients to attend. A new, time-efficient protocol within South Africa needs to be developed to assist in accommodating issues such as time off work.

Another factor to consider is African Traditional Healers, as they have a significant influence on people's behaviour when they seek help. de Andrade (2011) proposed that when

a clinician and client share the same values, this may evoke confidence of the patient towards health practitioners. This article further explains that in order to maximise health care programs, health practitioners need to be aware of as well as recognise and work within the patients' worldview. This view can be carried through to an ototoxicity monitoring program. The audiologist or counsellor needs to recognise the belief system of patients, specifically in relation to TB and hearing loss. Another study by de Andrade (2015) noted that patients might believe the hearing loss is a curse, and in this case, not because of the medication. This is important to assist with retention of patients with TB treatment, and with the ototoxicity monitoring program. By understanding their belief system, one can counsel the patient around this, without 'chasing' the patient away.

Furthermore, South Africa has 11 official languages which can impact the treatment and monitoring protocol. In conjunction with this, many patients receive DR-TB treatment in South Africa from other countries. Even within the small sample size of this current study, two participants were from neighbouring countries, which contributes to further language barriers. This is extremely difficult for counselling, as the above factors mentioned seem to be imperative for patient retention, and thus for a successful ototoxicity monitoring program. It also needs consideration for necessary testing, when instructing and counselling the patient. Thus, although not ideal, interpreters are essential, even if they interpret electronically, such as via Skype, to make it more feasible.

The number of audiologists available in South Africa needs to be taken into consideration. There are not enough audiologists to service this population, and many areas have no audiologists at all. This research used an extremely trained nurse to conduct the testing. At present, the current policy in South Africa is for nurses to conduct the automated audiometric testing (Koekemoer, n.d). However, the training of these nurses is insufficient, which only includes the basics of PTA, such as placement of the headphones, operating the

software, and patient requirements to complete the test. The success of this program is questionable (upon personal observation and personal communication with nurses conducting the tests as well as audiologists within the field). Therefore, for the initiation of a successful ototoxicity program countrywide, in-depth training of nurses to conduct at least otoscopy, immittance audiometry, PTA and DPOAE testing is essential. These nurses need adequate training in counselling of patients as well.

Lastly, during the study period, it was noted that medical doctors were required to understand audiological results. Also, the audiologists were required to recommend dosage adjustments based on hearing loss. Moreover, in some instances, audiologists were not present, and so nurses were required to assist. Yet there was no set protocol for evaluating hearing for ototoxicity and what was considered a considerable hearing loss to motivate for dosage or drug changes (Khoza-Shangase & Stirk, 2016). At different hospitals, various frequencies are tested, making uniformity between hospitals difficult; in that, some hospitals have ultra-high frequency audiometers, and some have standard audiometers. Based on the varying equipment found at different hospitals, and elements found in the study, the researcher, therefore, proposes a method for healthcare professionals to identify significant hearing loss and recommend whether dosage changes should be considered.

This method aims to be user-friendly with the use of a mobile application called Otocalc; an ototoxicity calculator which calculates significant hearing loss and provides recommendations.

8.2. Proposed ototoxicity monitoring protocol and procedures

An ototoxicity monitoring system has been designed specifically for the DR-TB population in South Africa. It is specific for this population as it includes aspects specifically

relevant to the patients and in line with the NDoH DR-TB treatment guidelines. The system includes counselling, interdisciplinary implementation, a proposed grading system and mobile application as well as an ototoxicity monitoring protocol.

8.2.1. Settings

This monitoring protocol acknowledges the limited resource settings. The mobile application was designed to be low cost, and available to those in the field. However, the correct equipment still needs to be available to test.

In an ideal setting, the audiometric equipment would be available, including UHF PTA and DPOAEs. Further, there would be an audiologist available to assist the nurses, mostly with the management of the identified hearing loss, and to assist with issues that may arise.

However, in a limited resource setting, this protocol would still require essential audiometric equipment, such as an otoscope, tympanometer, and PTA audiometer. In reality, there are few audiologists available, and so a nurse would be present, without an audiologist, to implement this protocol. Referral to an audiologist would be necessary for management of the hearing loss identified.

8.2.2. Interdisciplinary Implementation

Management of patients with DR-TB requires interdisciplinary team management. This involves the communication between the ototoxicity team regarding the monitoring and management of the patient, and not the multidisciplinary team, where each practitioner works in isolation. The core team should include at least a doctor, audiologist, and nurse whereas a support team should include a pharmacist, occupational therapist, physiotherapist, social worker, dietician, interpreter and psychologist (NDoH, 2011). The management team should further include the patients themselves, family members and other support structures (Mohr

et al., 2015). Interpreters are also shown to increase participation in treatment (Jacobs, Shepard, Suaya & Stone, 2004).

However, specifically for the TB ototoxicity monitoring program and retention, the doctors, audiologists, social workers, and pharmacists are imperative. Furthermore, the support structure such as family and friends (Mohr et al., 2015) is advisable where possible to supplement the interdisciplinary team. Also, interdisciplinary communication in contrast to multidisciplinary is essential, and ototoxicity monitoring and management of a joined effort between these parties together.

8.2.3. Counselling

Research has shown that counselling can improve adherence to treatment programs (Liefooghe, Suetens, Meulemans, Moran & De Muynck, 1999; Peltzer, Friend-du Preez, Ramlagan & Anderson, 2010). This was seen in a TB treatment adherence study by Liefooghe et al. (1999) where adherence was improved with counselling at every study visit. Adherence was not improved significantly; however, the improvement was still noticed. Another study looked at adherence and counselling, in particular with regards to HIV treatment and found that the more social support, the greater the adherence, where the use of herbal medicine was associated with lower adherence (Peltzer et al., 2010). As many of the patients with DR-TB are HIV infected, as with the participants in this current study, the importance of counselling is highlighted.

Therefore, as counselling can improve adherence, it needs to be a vital component of the ototoxicity monitoring program. If a patient is not adherent to the TB treatment, it is unlikely he/she will be adherent to the monitoring program. Also, counselling needs to be conducted at every visit; as sometimes, especially initially upon diagnosis, the patient may feel overwhelmed and need repetition. The family members should also be included in this counselling. Counselling should cover:

- What is TB and why adherence and completion of treatment adherence are important?
- What is hearing loss?
- TB drugs may cause hearing loss.
- Signs and Symptoms of hearing loss.
- Communication with Hearing loss
- Rehabilitation procedures and success.
- Alternate belief systems of the patient regarding hearing loss and TB. This is important as some cultures may believe hearing loss is a curse.
- Alternate medications that the patient is taking or would like to take.
- Importance of support systems at home and feasibility of adherence. If a patient does not have food at home, the likelihood of them completing the treatment is reduced. In cases like these, the treatment team needs to be notified, and social grants need to be applied for.
- Questions and comments of the patient.

Because there may be language barriers, this counselling session should be recorded in the eleven official languages. Although this is not ideal, it will allow the patient to understand somewhat. Brochures should also be available in the 11 official languages for the literate patients.

When interpreters are available, the interpreter can ensure that the patient can communicate with the service provider, be it the audiologist, doctor or nurse. Jacobs et al. (2004) found that the use of interpreters, in the USA, resulted in significant increases in the uptake of preventive services, physician visits, and prescription drugs, suggesting that interpreter services improved patients' access to primary and preventive care for a moderate increase in cost. They further discussed interpreters as a financially viable method for

enhancing service delivery. However, the cost estimate was done in the USA, at $279 per person per year (Jacobs et al., 2004). Interpreters are recommended within the South African population, however, if the specific site does not have the budget, recorded counselling and brochures should be used.

Furthermore, support groups may also assist the patients. The psychosocial factors are imperative and are the core of treatment adherence and compliance. Bateganya, Amanyeiwe, Roxo & Dong (2015) discussed the benefits of HIV support groups on morbidity, retention in care, mortality and quality of life for a person living with HIV. They mention, however, that it is unclear whether this would be cost-effective given the paucity of studies (Batenganya et al., 2015)

8.2.4. Audiological monitoring

The audiological protocol includes patient identification (those patients at risk and taking ototoxic medication), and baseline testing (for kanamycin it is suggested that baseline is indicted within 72 hours of the first dose) administration, monitoring and follow-up tests. These follow-ups are recommended at intervals that would allow the detection of the earliest signs of ototoxicity

8.2.4.1. Risk factor identification.

Early identification of patient's risk factors may assist in guiding the frequency of testing and possible outcomes. Counselling can address these risk factors and the likelihood of patients losing their hearing based on the risk factors. This depicts the necessity for interdisciplinary work. A risk factor checklist (Table 8.1), as below, was incorporated in the mobile application.

Table 8.1

Potential Risk Factors Identification Checklist

Potential Risk Factors	Yes	No	Not sure	Details
Existing Hearing Loss				
Previous Ototoxic Agent, such as: • Antibiotics (aminoglycosides when given IV): gentamicin, amikacin, tobramycin, netilmicin, kanamycin, streptomycin, neomycin • Antibiotics (macrolides): clarithromycin, ketolides, erythromycin (2-4g per 24h, IV only), azithromycin, glycopeptide, vancomycin (IV) • Antibiotics (peptide): capreomycin • Salicylates (more than 6-8 tablets a day): aspirin • NSAIDs (more than 6-8 tablets per day): ibuprofen, indomethacin, naproxen, diclofenac, mephenamic acid • Quinine • Loop diuretics (only when IV): furosemide, bumetanide, torasemide, piretanide • Chemotherapeutic agents: cisplatin, carboplatin, oxaliplatin, deferoxamine, vinca alkaloids, vincristine, vinblastine, vinorelbine, cyclophosphamide, chlorambucil, melphalan, fosfamide • Antiretrovirals (potentially ototoxic)				
Renal problems or impaired hepatic function Subjective report of difficulty hearing (difficulty with TV, radio, restaurant, co-workers, clients, customers, friends, relatives, neighbours) Above 55 years of age Diabetes mellitus Family history of Hearing Loss Excessive noise exposure (works in music industry, in noisy factories) Previous illnesses such as cancer, meningitis, encephalitis, mumps, measles, chronic ear infections. Previous head injury				

8.2.4.2. Baseline Testing.

Baseline testing should be as comprehensive as possible. However, in limited resource settings, the minimum testing should include otoscopy, tympanometry (screening is sufficient), air conduction PTA (HF) from 0.25 kHz to 8 kHz (0.25, 0.5, 1, 2, 3, 4, 6, 8). Ideally, baseline testing should include otoscopy, tympanometry (screening is sufficient), air conduction from 0.25 kHz to 20 kHz (0.25, 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11.2, 12.5, 14, 16, 18 and 20 kHz), and bone conduction up to 6 kHz. If equipment is available, DPOAE testing should also be performed for follow-up ease of monitoring. Speech audiometry should be performed if possible. However, language differences must be noted. The recorded English and isiZulu wordlists should be used if available.

8.2.4.3. Follow-up monitoring (intervals and frequency range).

Intervals: monitoring twice a month (bi-weekly) is recommended in an ideal setting, however, if this is not possible, alternatively, the initial follow up should be two weeks post baseline, and monthly thereafter. This is recommended for the entire period that the patient receives treatment for DR-TB.

As PTA is generally used to grade hearing loss and as well as to direct the change of dosage and treatment adjustments, PTA's most considerable changes will mainly be used. Therefore, in the first three months of monitoring, it is recommended that baseline testing, as well as week 2 and week 6 undoubtedly be conducted. As week 4 and 8 showed the least change, the following test could be conducted at week 10 or 12. This would be for a limited resource setting, and ideally, testing should be conducted every two weeks. This schedule of an initial visit two weeks post baseline, and monthly thereafter often coincides with the general required doctor visits to the hospital. Subsequently, monitoring should take place every 3 months for a total of 6 months post-treatment. If there is a hearing loss, annual monitoring and management are recommended.

Frequency Range for follow-up testing: Follow-up should include limited frequency range, as patients tire easily. When UHF testing is available, testing can include 6 to 16 kHz (6 to 8 kHz and inclusive being HF, with 9 to 16 kHz being UHF). According to Fausti et al. (1999), the frequencies that showed the most significant sensitivity were 8, 9, 10, 11.2 and 12.5 kHz (generally separated by 1/6 octave. When high-frequency testing is not available, 3 kHz to 8 kHz should be safe. At the high frequencies, there is an abrupt decrease in hearing sensitivity already from youth. Hitherto, no international standard for 0 dB hearing level exists for frequencies above 8 kHz.

It is questioned whether a general standard is meaningful at all and that normative data for various age groups should instead be used as a reference level (Osterhammel & Osterhammel, 1978).

Table 8.2

Suggested time periods and frequencies for new ototoxicity monitoring protocol

Ideal Setting	Limited Recourse Setting	Frequency Range (PTA)
Baseline	Baseline	0.25 kHz to 20 kHz, where available
Week 2	Week 2	6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 4		6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 6	Week 6	6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 8		6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 10	Week 10	6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 12		6 kHz to at least 16 kHz when UHF equipment available. 3 kHz to 8 kHz when HF equipment available
Week 14	Week 14	0.2 5 kHz to 20 kHz when UHF equipment available 0.25 kHz to 8 kHz when HF equipment available
Biweekly (if ototoxicity identified)	Monthly (if ototoxicity identified in limited recourse setting)	-6 kHz to at least 16 kHz when UHF equipment available. -3 kHz to 8 kHz when HF equipment available -0.25 kHz to 20 Hz every three months
Monthly (if no ototoxicity detected)	Monthly (if no ototoxicity detected)	-6 kHz to at least 16 kHz when UHF equipment available. - 3 kHz and above when HF equipment available -0.25 kHz to 20 kHz at the conclusion of the injectable period

Ideal Setting	Limited Recourse Setting	Frequency Range (PTA)
3 monthly for a total of 6 months (post treatment)	3 monthly for a total of 6 months (post-treatment	-6 kHz to at least 16 kHz when UHF equipment available. -3 kHz w to 8 kHz hen HF equipment available -0.25 kHz to 20 kHz where UHF equipment available at the conclusion of this 6-month period --0.25 kHz to 8 kHz when HF equipment available at the conclusion of this 6-month period

Note: should the hearing loss progress to 6 kHz with UHF, or 3 kHz with HF monitoring, the lower frequencies must be tested as well

DPOAEs: When the patient is not responsive, DPOAE monitoring alone can be done. High-frequency diagnostic DPOAEs should be done, with ambient noise less than 55 dBA SPL. Repeat readings must be done at every measure, and a significant change can be considered 6 dB.

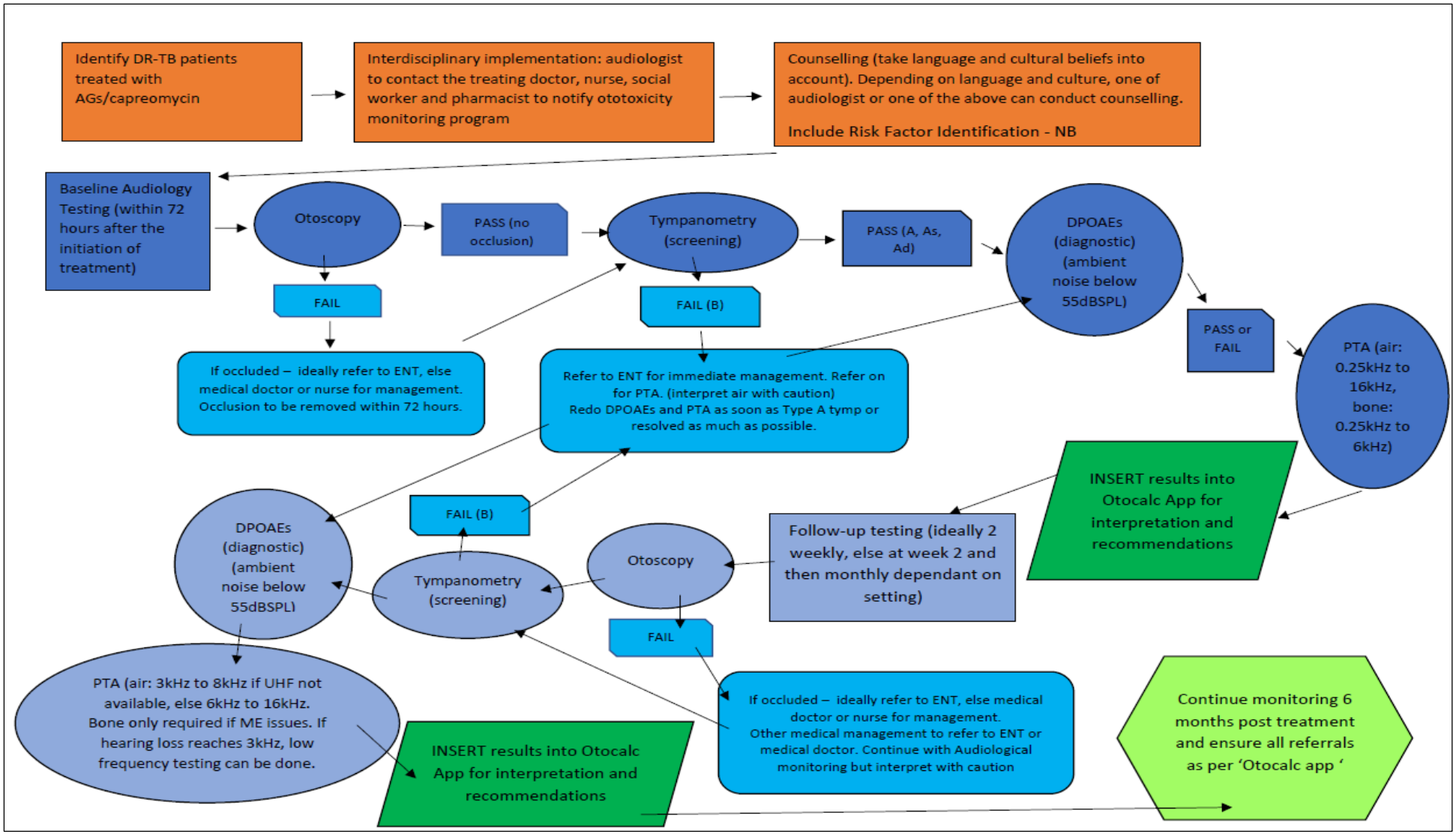

Figure 8.1. Basic flowchart for ototoxicity monitoring of DR-TB patients

8.3. Proposed Grading System with Mobile Application

8.3.1. Proposed Grading System with Mobile Application

A grading system provides a systematic framework to classify loss of hearing from baseline. It allows a clear understanding of the degree of this loss and assists with methodical and uniform management.

From observation and individual consultation with medical doctors in the field, many are unable to interpret audiograms when provided. Hearing loss guides the motivation for changes in the treatment regimen. These changes in the treatment regimen may involve the doctor changing the drug and perhaps reducing the days of therapy, and thus, it is essential that the doctors and nurses understand the correct interpretation of audiograms in order to implement these changes, as well as for the counselling of the patients.

It is generally the audiologists' role to interpret audiograms; however, audiologists are often not available TB management clinics. If a trained nurse, as recommended above will be conducting audiological testing, a grading system will assist in the interpretation. This will guide the management protocol.

Also, many audiologists are unsure how to classify a significant ototoxic hearing loss, and when to advise the medical doctor to adjust the medication regimen.

Therefore, through this research, the development of a mobile application was developed to assist in the classification of hearing loss and guide the management. This application acts as an 'ototoxicity calculator'. This application will be discussed further is 8.3.2

The purpose of this mobile grading system is two-fold. Firstly, it can assist the health professional in assessing the patient for ototoxicity as well as establishing the clinical significance of this ototoxicity. Secondly, it can be used for ongoing care by the healthcare

professional, who will update the variable component of the application at each visit to monitor the progression of hearing loss. This system provides a systematic basis for referral and management of patients according to their needs.

This 'otocalc' application acts as an 'ototoxicity calculator'.

There are two avenues in which this application can be used:

1. Ototoxicity Calculator: the doctor/nurse/audiologist can access the application, enter the baseline and follow up pure tone audiograms, and subsequently the application will provide the correct grade of hearing loss as well as possible recommendations. This can be used as a 'once off' calculation, and patient details are not stored on the system. The user does not need to register for this option.
2. Ototoxicity Monitoring Application: this would be available to those working within the field of TB, specifically DR-TB management. Those conducting the audiograms or receiving the completed audiograms (for example the doctor) would enter the patient's results. These results can be uploaded to a database. The reasoning for this is should a patient be transferred to another hospital or area, the doctor in that area will be able to access the patients' audiology results. However, only healthcare professionals working in this field and registered on the application would be granted access to the database. Moreover, access to individual patients can only be obtained with the patients' identity number and/or hospital number, as it would be unethical for a professional not working with the patient to access his/her results. This limited access page will also act as an ototoxicity calculator.

8.3.2. Development of 'Otocalc'

The development of this mobile application took approximately one year, where the developer and the audiologist worked in the application to make it user-friendly and relevant to diverse healthcare professionals.

Various professionals were involved in the development of the application. These professionals included a software engineer who built the application, an audiologist and the researcher who designed the application. Various healthcare professionals, including a pharmacist, medical doctor and two audiologists (one involved in the field, as well as an audiologist on private practice) were involved in piloting the application and advising on suggested changes.

These changes included multiple user accessibility modifications and changes with the 'recommendations' framework as well as additions and deletions of aspects such as the risk identification checklist, storage of the data on the database, and grading descriptions. From initial development, the app underwent 14 modifications, until it was ready for upload on the Android and iOS stores for download. It will be uploaded to these stores once approval is obtained by the university.

8.3.3. Newly Developed Grading System

The calculator contains the grades as per table 8.3, with interpretation and recommendations. Counselling should be conducted as per 8.2.3; however, a summary is included in the recommendation column. As UHF is often not conducted, the majority of individuals would present with either a grade three and above, or hearing that is not gradable (no ototoxicity). When the hearing presents as grade three, the loss in hearing is likely interfering with daily functioning.

Table 8.3

Mobile application grading system: grade, description, explanation & recommendations as used in the 'otocalc' mobile application

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
1	10 dB or greater change in thresholds at two or more ultra-high frequencies (9 kHz to 20 kHz) from baseline in at least one ear	• The patient will likely not notice a deterioration of hearing abilities. • It is the early stages of hearing loss, but it is not yet affecting the frequency range of speech sounds (250Hz – 8 kHz). • It is possible that should the patient continue with the current drug regimen; the hearing loss may progress to speech frequencies.	**Goal:** Possible prevention or reduction of clinical hearing loss through early identification. **Team:** **Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug. **Audiologist or nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • A follow-up appointment in 2 weeks for repeat audiogram.	**Goal:** Possible prevention or reduction of clinical hearing loss through early identification. **Team:** **Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug. **Audiologist or nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • A follow-up appointment in 2 weeks for repeat audiogram.
2	20 dB or greater change in	• The patient will likely not notice a deterioration of hearing	**Goal:** Possible prevention or reduction of clinical hearing loss through early identification. **Team:**	**Goal:** For patients to understand the nature and implications of hearing loss, but also the implications should they refuse treatment. It is

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
	thresholds at more than two frequencies in ultra-high range (9 kHz to 20 kHz) from baseline in at least one ear	abilities unless he/she is a musician. • This is a significant loss of cochlear hair cell function in the ultra-high frequencies that are not yet affecting the frequency range of speech sounds (0.25 kHz – 8 kHz). It is possible that should the patient continue with the current drug regimen; the hearing loss may progress to speech frequencies.	**Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug. **Audiologist or nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • A follow-up appointment in 2 weeks for repeat audiogram.	important that patients feel supported and not alone. **Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • Amplification devices (e.g. hearing aids) are available if hearing loss is identified. • Discuss and address the fears and concerns of the patient and family members.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
				• Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss. The patient should report any change in medical and hearing status to health professionals.
3	10 dB or greater change in thresholds into two frequencies from 8 kHz and below from baseline in at least one ear	• The hearing loss is now in the speech frequency range. • Depending on the patients' listening demands and processing abilities, the hearing loss may affect his/her day to day functioning. • The patient may hear people talking, however, may not always be able to discriminate the words spoken, for example 'eight versus fate'.	**Goal:** The identification of early clinical hearing loss, and exploration or alternative treatment to prevent/ reduce further hearing loss and functional impairment. **Team:** **Medical doctor:** • Consider dosage adjustment • Consider the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug.	**Goal:** For the patients to understand hearing loss, as well as its possible management in the future. It is important for patients to understand that DR-TB treatment is imperative, despite the hearing loss; but also, that they are not alone, and management is possible. **Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
		• The patient will likely also struggle to discriminate speech in the presence of background noise.	• Refer to audiologist for diagnostic audiological assessment. **Audiologist:** • Conduct diagnostic audiological assessment. • Consider hearing amplification for future. • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. A follow-up appointment in 2 weeks for repeat audiogram.	• Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss (try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available if hearing loss is identified. • Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss.The patient should report any change in medical and hearing status to health professionals.
4	10 dB or greater change in	• The hearing loss is now in the speech frequency range.	**Goal:** The identification of early clinical hearing loss, and exploration or alternative treatment to prevent/ reduce further hearing loss	**Goal:** For the patients to understand hearing loss, as well as its possible management in the future. It is essential for patients to understand

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
	thresholds in any 3 or more frequencies from 8 kHz and below from baseline in at least one ear	• Depending on the patients' listening demands and processing abilities, the hearing loss may affect his/her day to day functioning. • The patient may hear people talking, however, may not always be able to discriminate the words spoken, for example 'eight versus fate'. • The patient will likely also struggle to discriminate speech in the presence of background noise. .	and functional impairment. Audiological management can be considered. **Team:** **Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Audiologist:** • Conduct diagnostic audiological assessment. • Consider hearing amplification. • Discuss communication strategies with the patient and his/her family.	that DR-TB treatment is imperative, despite the hearing loss; but also, that they are not alone, and management is possible. Patients need to start understanding the process of amplification. **Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
			• Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. A follow-up appointment in 2 weeks for repeat audiogram.	(try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available. • Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss. • The patient should report any change in medical and hearing status to health professionals.
5	20 dB and above change in thresholds at 3 frequencies or more at 8 kHz or below from baseline in at least one ear	• This hearing loss is affecting the patients' ability to hear, discriminate and understand speech. • The hearing loss is likely to affect the patient considerably in communicating at	**Goal:** The prevention or reduction of further hearing loss by treatment adjustments/changes. The audiological team can consider amplification. **Team:** **Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug.	**Goal:** For the patients to understand hearing loss, as well as its possible management in the future. It is important for patients to understand that DR-TB treatment is imperative, despite the hearing loss; but also, that they are not alone, and management is possible. Patients need to start understanding the process of amplification. **Team:** **All health professionals should discuss the following with the patient and his/her family:**

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
		home, work and with family or friends. • The patient will struggle significantly to hear speech in noisy situations. • The hearing difficulties may affect the patient socially and emotionally.	• Refer to audiologist for diagnostic audiological assessment. **Nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Audiologist:** • Conduct diagnostic audiological assessment. • Consider hearing amplification. • Discuss communication strategies with the patient and his/her family. • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. A follow-up appointment in 2 weeks for repeat audiogram.	• The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss (try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available. • Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
				relevant to the management of hearing loss.The patient should report any change in medical and hearing status to health professionals.
6	More than 40 dB change in threshold in up to 2 frequencies from 8 kHz and below from baseline in both ears	• This hearing loss is affecting the patients' ability to hear, discriminate and understand speech. • The hearing loss is likely to affect the patient considerably in communicating at home, work and with family or friends. • The patient will struggle significantly to hear speech in noisy situations. • The hearing difficulties may affect the patient	**Goal:** Treatment changes are imperative. And audiological management is essential at this stage, if possible. **Team:** **Medical doctor:** • Consider dosage adjustment. • Consider the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment.	**Goal:** The patient must understand that if he/she stops treatment, the hearing will not recover, and it will have life-threatening implications. The patient must start coming to terms with the possibility of losing their hearing entirely, and its life-changing implications ahead. **Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
		socially and emotionally.	**Audiologist:** • Conduct diagnostic audiological assessment. • Consider hearing amplification. • Discuss communication strategies with the patient and his/her family. • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. A follow-up appointment in 2 weeks for repeat audiogram.	• Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss (try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available. • Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss. The patient should report any change in medical and hearing status to health professionals.
7	More than 40 dB change in thresholds at 3 or more frequencies from 8 kHz	• This hearing loss is affecting the patients' ability to hear, discriminate and understand speech.	**Goal:** Treatment changes are imperative. And audiological management is essential at this stage, if possible. **Team:** **Medical doctor:** • Consider dosage adjustment.	**Goal:** The patient must understand that if he/she stops treatment, the hearing will not recover, and it will have life-threatening implications. The patient must start coming to terms with the possibility of losing their hearing altogether, and its life-changing implications ahead.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
	and below from baseline both ears	• The hearing loss is likely to affect the patient considerably in communicating at home, work and with family or friends. • The patient will struggle significantly to hear speech in noisy situations. • The patient will struggle significantly to hear in small group situations. • The patient will struggle significantly with one-to-one conversation. • The hearing difficulties may affect the patient socially and emotionally.	• Consider the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Nurse:** • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug. • Refer to audiologist for diagnostic audiological assessment. **Audiologist:** • Conduct diagnostic audiological assessment. • Consider hearing amplification. • Discuss communication strategies with the patient and his/her family. • Inform the medical doctor of the change in thresholds. • Motivate for dosage adjustment. • Motivate for the use of an alternate non-ototoxic drug.	**Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss. • Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss (try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
			• A follow-up appointment in 2 weeks for repeat audiogram.	• Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss.The patient should report any change in medical and hearing status to health professionals.
8	Hearing thresholds at 80 dB or greater in 4 or more speech frequencies (250 Hz to 8 kHz) in both ears	• The patient has now lost most of his/her hearing. • The patient will most likely be unable to communicate with family, friends and colleagues effectively. • The patient will, as a result, be isolated in various ways, specifically in social and occupational situations.	**Goal:** Cochlear implant consideration and referral audiological considerations for long-term management. **Team:** **Medical doctor and nurse:** • Refer to an audiologist for aural rehabilitation.	**Goal:** This is an extremely vulnerable place for patients, as they are often entirely isolated. It is important they understand that they are not alone and that there are still options for jobs and life in the Deaf world. Facilitation into this 'Deaf' world needs to be guided, addressing all the fears and concerns. **Team:** **All health professionals should discuss the following with the patient and his/her family:** • The possibility that some drugs used in the treatment of TB may cause a hearing loss. • Importance of adherence to treatment despite the potential hearing loss.

Grade	Description	Interpretation	Management recommendations	Recommendations for counselling
		• Depending on the patient's job, it is possible that he/she will be unable to continue work due to the hearing disability.		• Hearing loss is not always preventable but that a motivation for the alternate non-ototoxic drug will be done. • Hearing loss will in most cases be permanent. • Hearing loss may impact on their communication abilities are home, work and with family or friends. • The patient is not alone, and there are others who are also suffering from this hearing loss (try and put patients in touch with each other for support). • Amplification devices (e.g. hearing aids) are available. • Discuss and address the fears and concerns of the patient and family members. • Provide the patient and his/her family with all the medical and audiological options relevant to the management of hearing loss. The patient should report any change in medical and hearing status to health professionals.

8.3.4. Steps to use the mobile application: 'otocalc'

The mobile application will be downloadable on all android devices and iPhones. The application name, 'otocalc' will be explained in various steps.

8.3.4.1. Step 1.

Step 1 is the introduction and registration of the application.

The four images below include the steps from downloading the application, to the home page where the user can register on the application.

Once the user is on the homepage (Figure 8.2d), they can further re-read the purpose of the application, by clicking onto the 'about' section, it will explain the purpose and use of the application. Then a registered user can sign in. Alternatively, a healthcare professional can register as a user. Or, the application can be utilised as a once off calculator to calculate the significance of possible ototoxicity.

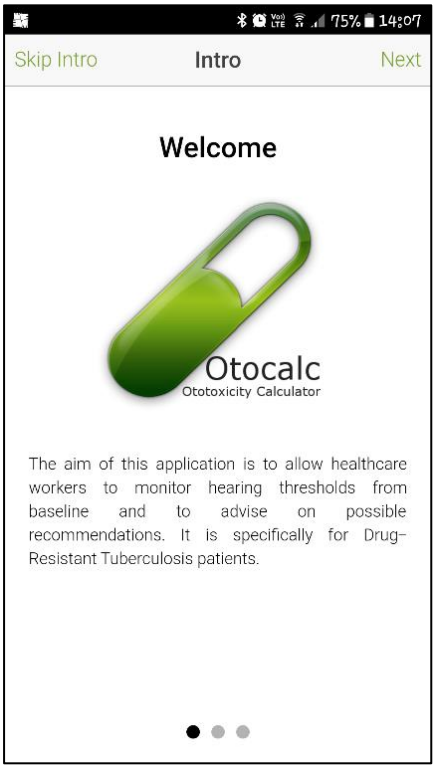

Figure 8.2a. First page after download.

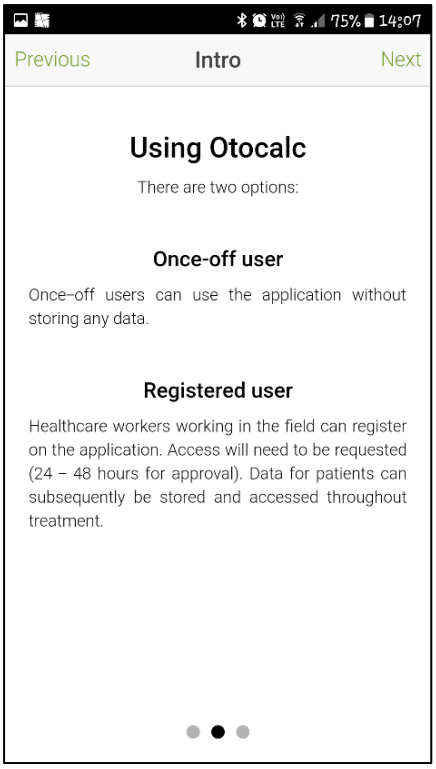

Figure 8.2b. Description of the application.

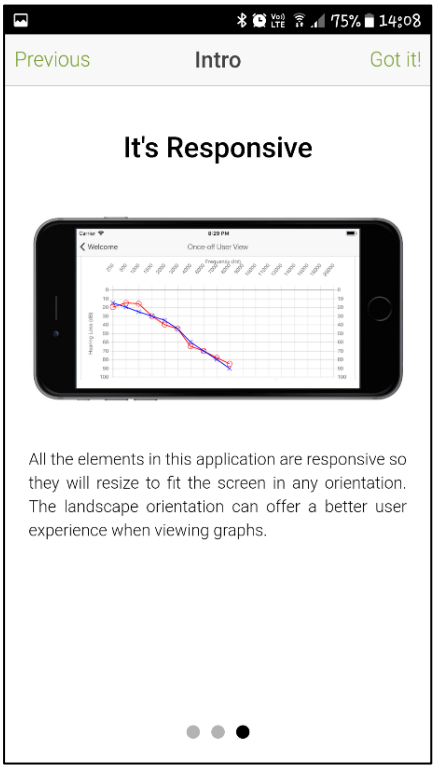

Figure 8.2c. Explanation of 'otocalc' feature.

Figure 8.2d. Otocalc home page.

8.3.4.2. Step 2.

Should the healthcare professionals wish to register as a user, they will be directed to the page as per Figure 8.3. This page is to ensure that only health care professionals within the field will have access to patient data, to ensure ethical practice of this application and patient confidentiality. The potential user will be requested to enter their information as per Figure 8.3. This information will be sent to the mobile application administrator, who will assess the request, and either grant or decline access (Figure 8.4). Access will be based on a valid HPCSA number (where relevant), occupation must be relevant to the use of the app (audiologist, pharmacist, doctor, counsellor, occupational therapist, physiotherapist, social worker, nurse and psychologist) and lastly, the healthcare professional must be working in an institution that treats DR-TB patients in the public or private sector. Once access is granted, the user will be able to set their password, and subsequently sign in as a registered user.

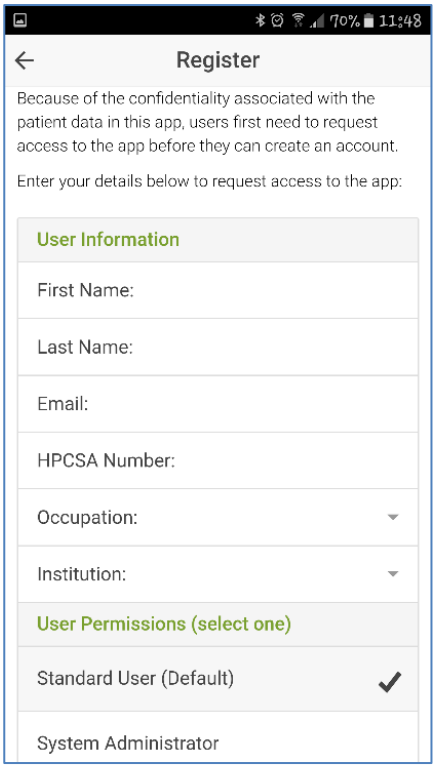

Figure 8.3. Health professional registration page.

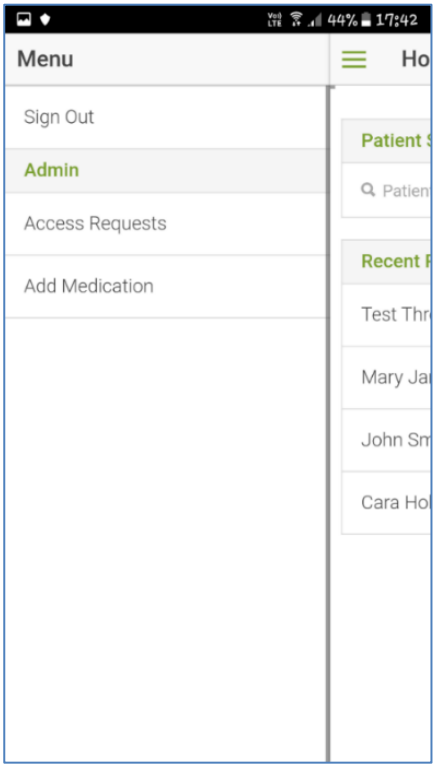

Figure 8.4. Administrators access request page.

8.3.4.3. Step 3.

Once the user signs in, they can either enter details regarding a new patient, enter new data about existing patients as a new visit, or search for results of another patient. The user would need to enter the ID or hospital number of a patient in order to access their details. This would be in the case that a patient is referred to another clinic or treatment site that would like to access the patients' previous audiological data.

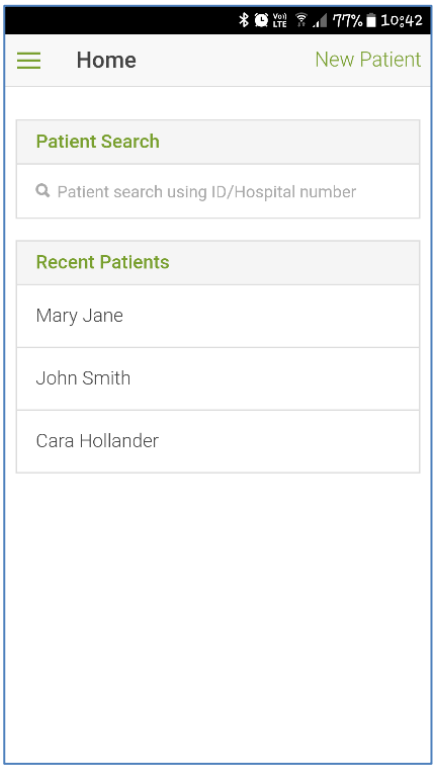

Figure 8.5a. New patient identification entry page.

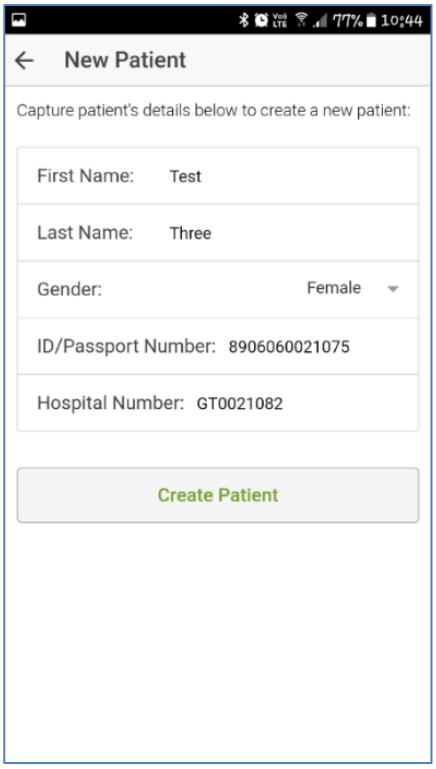

Figure 8.5b. Continuation of new patient identification entry page.

8.3.4.4. Step 4.

Once the user selects the participant, they will be directed to a page as per Figure 8.6. All the patients and names used are aliases, and are not actual patients, yet used for the purpose of this explanation.

The user must choose the ‘new consultation’ tab and enter the information as in Figure 8.7.

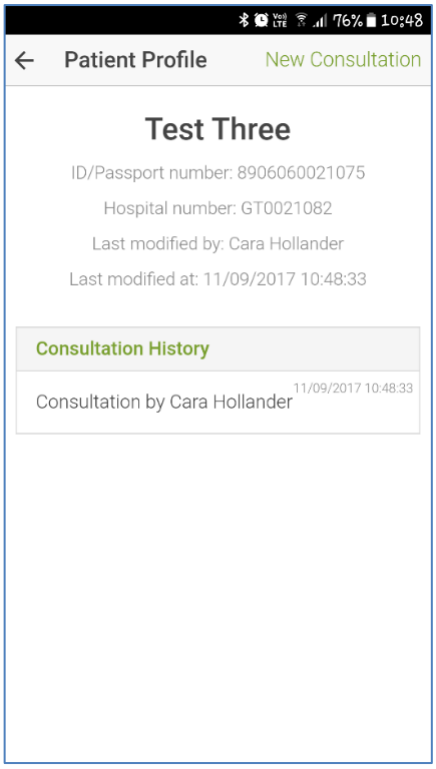

Figure 8.6. Patient home page once identification data has been entered.

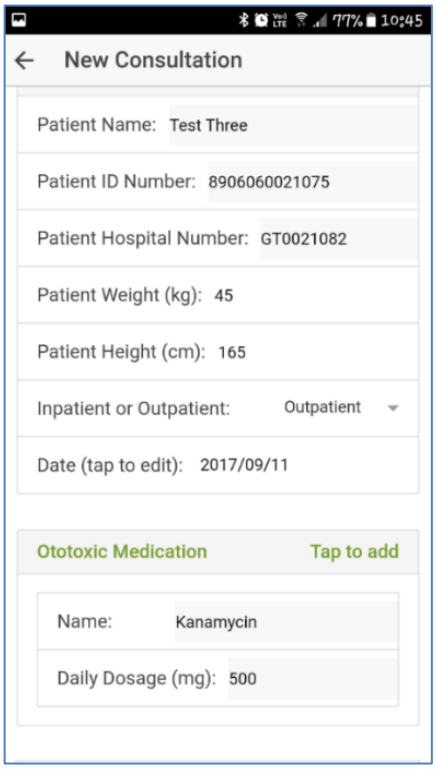

Figure 8.7. New consultation home page for patient data entry.

The user can subsequently enter details on the risk factor checklist (Figure 8.8a), by choosing ‘tap to edit’ tab by the risk factor checklist (Figure 8.8a)

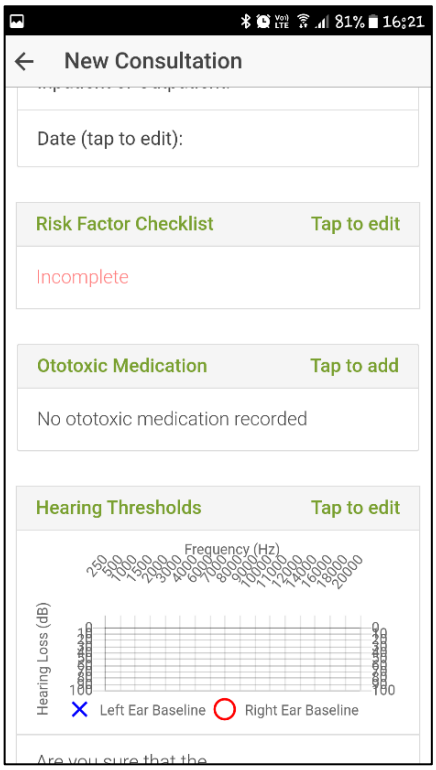

Figure 8.8a. Tab for risk factor checklist.

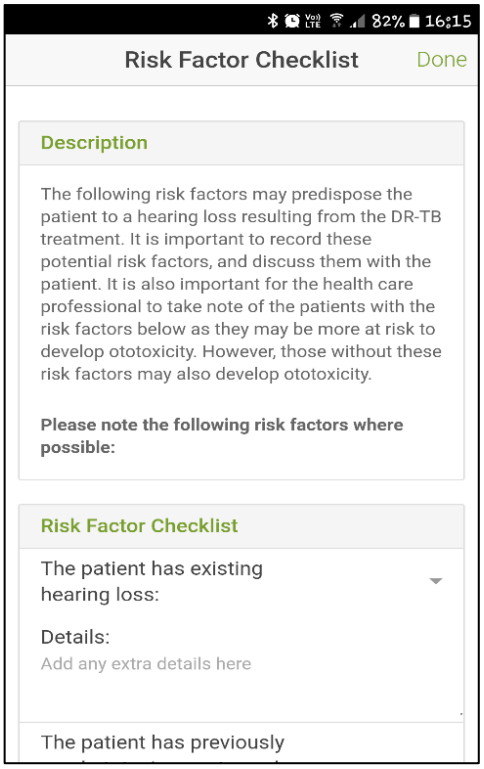

Figure 8.8b. Risk Factor Checklist

The page as per Figure 8.9a appears when the user chooses the on ‘tap to edit’ by the hearing thresholds as per Figure 8.8. Figure 8.9b, however, contains the already entered results from the baseline.

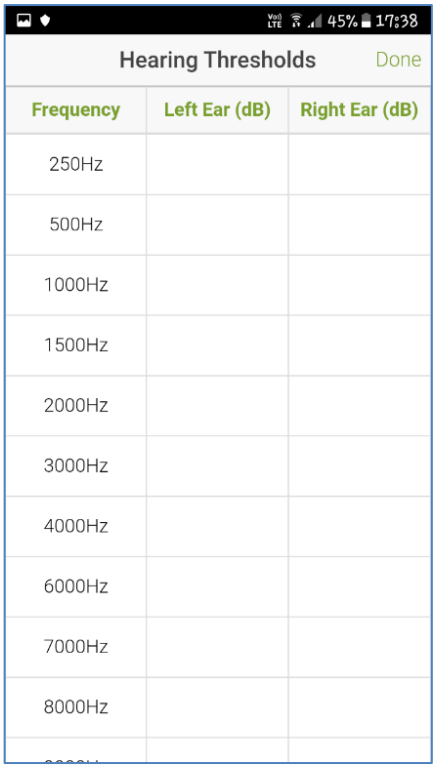

Figure 8.9a. PTA threshold entry page

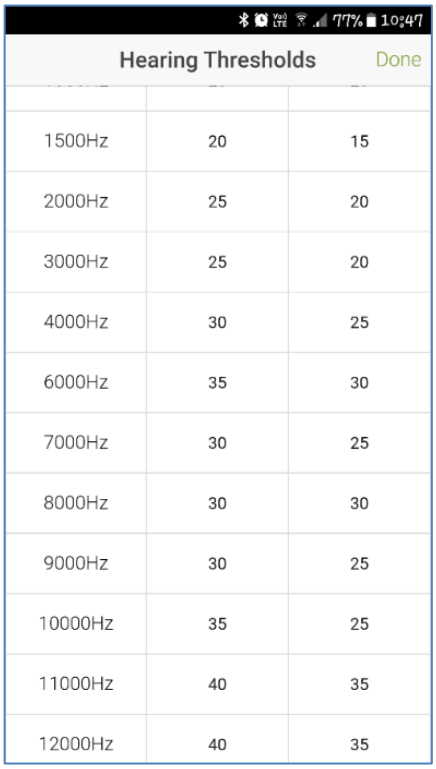

Figure 8.9b. Continuation of PTA threshold entry page

Once the thresholds are entered, the application plots the audiogram (see Figure 8.10)

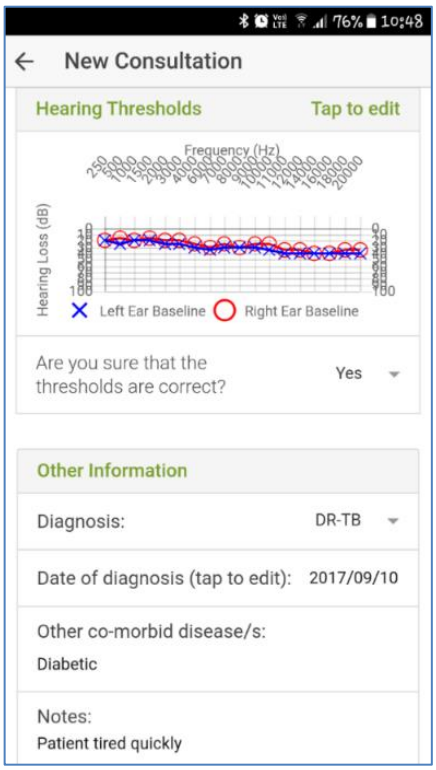

Figure 8.10. Audiogram plotted based on thresholds entered

8.3.4.5. Step 5.

Once the user has entered all the baseline data and saved it, he will be directed to the page as per Figure 8.11. For the follow-up visits, the user needs to choose the relevant patient, in this case, ‘Test Three’ (Figure 8.11) and then go to ‘new consultation’ (Figure 8.12)

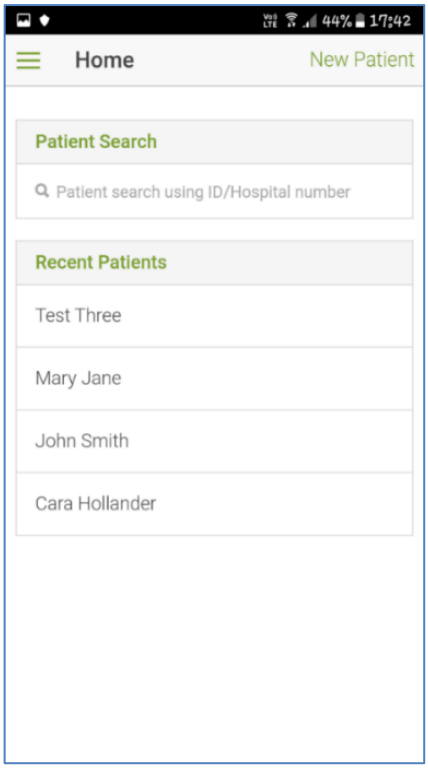

Figure 8.11. Homepage after baseline consultation has been saved

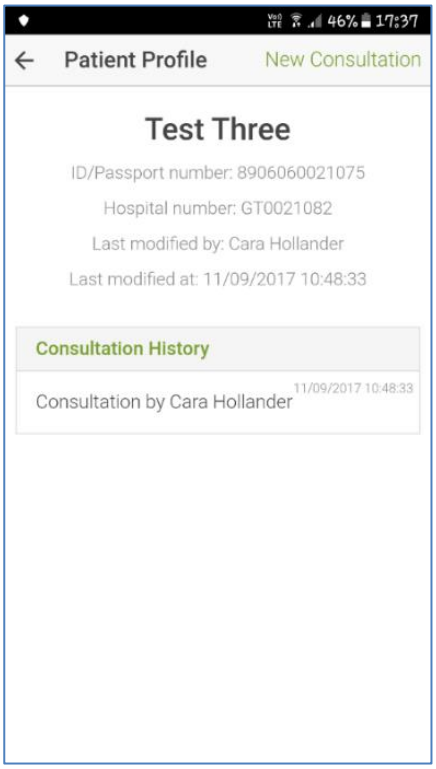

Figure 8.12. Homepage of patient 'test three' for new consultation to be initiated

8.3.4.6. Step 6.

In this case, the baseline data has already been entered, and the follow-up data can now be entered. The user would be required to update the patient details, as well as weight, height, and drug information where possible. The entering of the data is the same as per the baseline data (Figures 8.13, 8.14a and 8.14b).

The user would subsequently enter the follow-up results in a similar fashion to the entry of baseline results. It would then be plotted automatically on an audiogram. If the user rotates their phone screen, the audiogram is clearer.

Should the user only be using this application as an ototoxicity calculator, he/she will be directed to a page like this to enable the entering of baseline and follow-up data. It would grade the hearing loss and provide with recommendations. Other information is not required, and data is not saved to a database.

Figure 8.13. Follow up patient data entry page

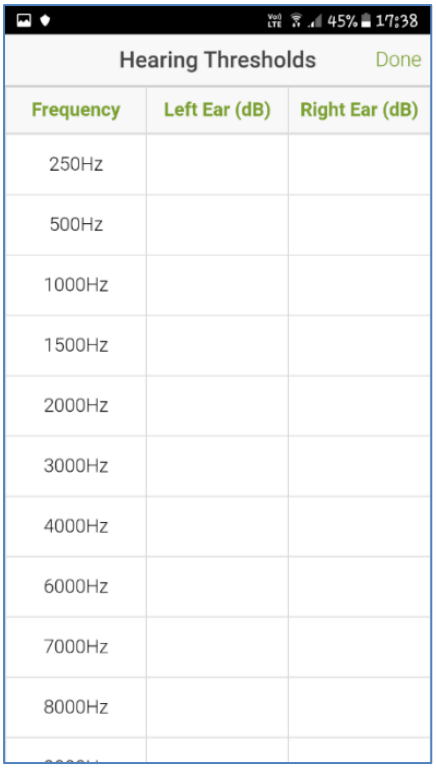

Figure 8.14a. Follow -up PTA threshold entry page

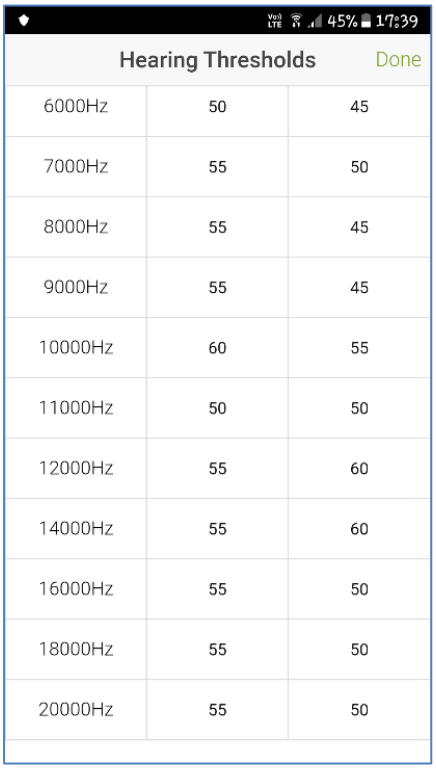

Figure 8.14b. Continuation of follow -up PTA threshold entry page

8.3.4.7. Step 7.

Once baseline and follow-up audiological data have been entered, the results will be calculated, as per the yellow block in Figure 8.15. When the user taps the yellow block, the description and recommendations as per Table 8.2 will be displayed.

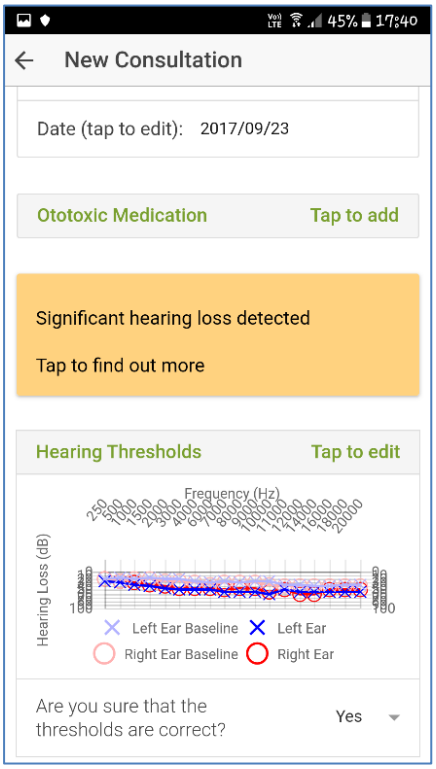

Figure 8.15. Page, when follow up consultation, has been entered and results calculated

8.3.4.8. Step 8.

The user can scroll down the recommendations, after choosing the yellow block, as per Figures 8.16, 8.17a, 8.17b, 8.17c.

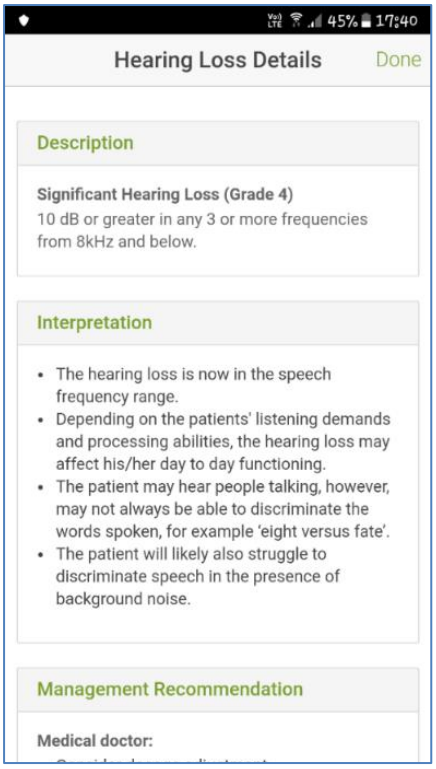

Figure 8.16. Interpretation and recommendation based the yellow block

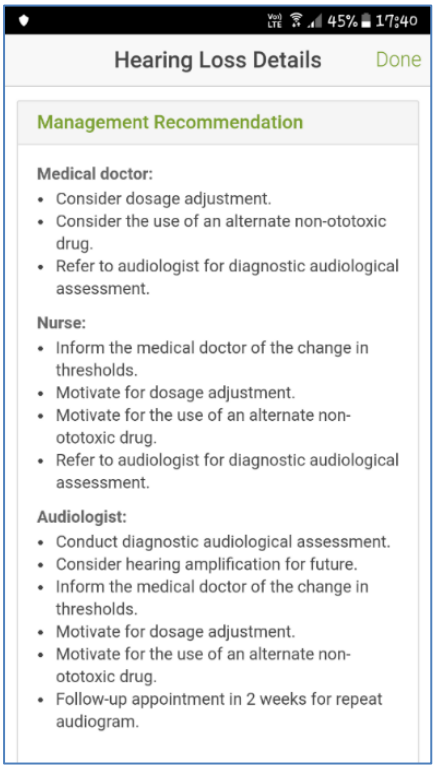

Figure 8.17a. Recommendation for patient

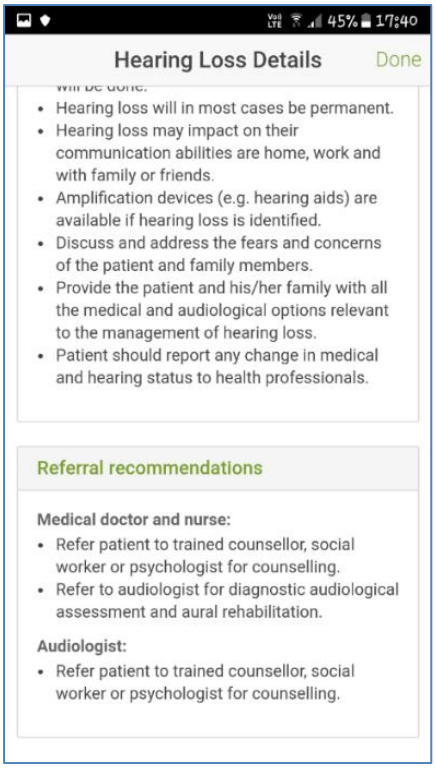

Figure 8.17b. Continuation of recommendations

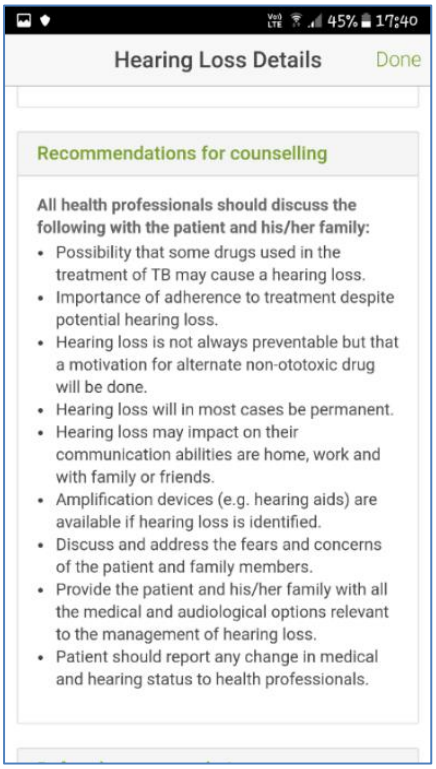

Figure 8.17c. Continuation of recommendations- final page

8.3.4.9. Step 9.

For every new consultation, patient data can be updated or changed Figure 8.18.

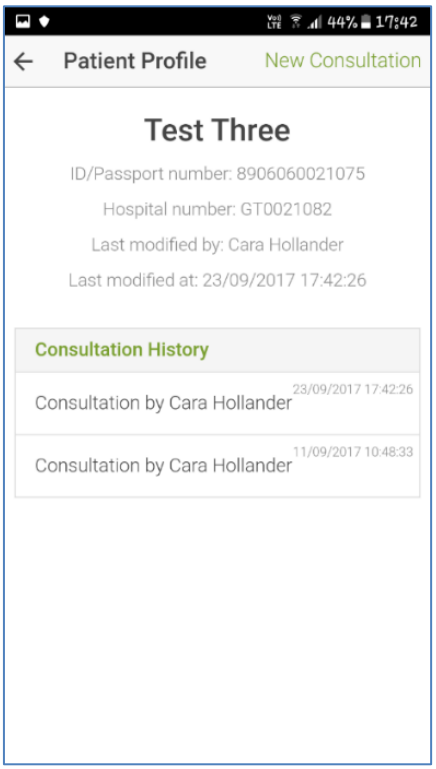

Figure 8.18. Homepage once follow-up data has been entered, interpreted and saved

8.3.4.10. Conclusion.

All this data is saved onto a database which can be used for reliable statistics and research. This can only be done if permission is obtained from the patient, gatekeeper and ethical clearance from the relevant organisation.

8.3.5. Sensitivity of 'Otocalc'

The data from this current study was used to establish the sensitivity of 'Otocalc'. The sensitivity of Otocalc was compared to the existing grading systems. When using Otocalc, ototoxicity was identified in all, but two ears (participants 2 and 4). This is more than the other scales (Table 8.4). However, the grades also give an indication of the frequencies

affected, in order for understanding; for example, a grade 3 indicates a loss in the high frequencies and not UHF, whereas grades 1 and 2 indicates UHF hearing loss.

Table 8.4

Sensitivity of 'Otocalc'

Patient	Weeks in the Study (T)	EAR	'Otocalc'	TUNE	CTCAE	ASHA
1	0,1,2	R	**2**	2a	-	YES
		L	**2**	1a	-	YES
2	0,1	R	**2**	0	-	NO
		L	**0**	1a	-	NO
4	0,1,2,3,4,5,6	R	**3**	1a	-	YES
		L	**0**	0	-	NO
5	0,1,2,3,4,5,6	R	**1**	1a	-	YES
		L	**3**	2a	-	YES
6	0,1,2	R	**1**	0	-	YES
		L	**2**	0	-	YES
7	0,1,2,3,4,5,6	R	**2**	2a	-	YES
		L	**1**	0	-	YES
8	0,1,2,3,4,5,6	R	**2**	2a	-	YES
		L	**1**	1a	-	YES
9	0,1,2,3,4,5,6	R	**3**	1a	-	YES
		L	**1**	1a	-	YES
10	0,1,2,3,4,5,6	R	**3**	2a	-	YES
		L	**1**	2a	-	YES
12	0,1	R	**3**	2a	1	YES
		L	**1**	1a	-	YES

Patient	Weeks in the Study (T)	EAR	'Otocalc'	TUNE	CTCAE	ASHA
14	0,1,2,4	R	**1**	1a	-	YES
		L	**3**	1a	-	YES
15	0,1,	R	**3**	1a	-	YES
		L	**4**	1a	-	YES
16	0,1,2,3,4	R	**1**	2a	-	YES
		L	**3**	1a	-	YES
17	T0, T1, T2, T3, T4	R	**5**	2a	-	YES
		L	**3**	1a	-	YES
18	0,1,3,4,5,	R	**1**	1a	-	YES
		L	**2**	2a	-	YES

8.4. Need for further research

This newly developed application needs to be trialled by various health care professionals, such as doctors, nurses, pharmacists and audiologists within the DR-TB population. It has the potential to standardize monitoring and dosage adjustments based on hearing, while also allowing for reliable statistics and follow-up of the patients on a single database throughout the country.

Chapter 9: Conclusion

This chapter will conclude the thesis, with the provision of a summary of the study results and outcome as well as the strengths and the limitations of the findings. The study's implications will be discussed with further recommendations for research, and lastly, the thesis will be concluded.

9.1. Summary of the Findings

9.1.1. Audiological Results

The audiological results and discussion address the aim of determining the changes in hearing levels in patients undergoing treated with kanamycin and capreomycin for DR-TB; by looking at the prevalence of abnormal findings on baseline assessments and determining the change in hearing levels from baseline.

Upon discussing the PTA and DPOAEs, a definite pattern was observed which indicated the ultra-high frequencies being affected first, and more so within the first three months than the conventional audiogram. The findings also highlighted the lack of grading scales developed for high-frequency testing, specifically in the DR-TB population. The identification of the UHF and high-frequency hearing loss highlights the possibility of ototoxicity monitoring only from 3 kHz and above, in order to save time, with baseline testing from 0.25 kHz in order to assist with management as well as to rule out other possible influencing factors.

Furthermore, the evidence of replacing the PTA with DPOAEs is not substantial, as correlation is not definitive. Although the use of DPOAEs for monitoring ototoxicity would

be ideal, as they detect extremely small changes prior to PTA as well as they are quicker and require less patient participation, more research needs to be conducted in this area.

Also, asymmetry was noted in this current study, in contrast to the bilateral and symmetrical configuration that has been previously understood. Moreover, although kanamycin appeared to be more ototoxic in this study, as well as in other studies, more details should be obtained on the toxicity profile of capreomycin in patients with DR-TB, in order to rationalise the possible implementation of this more expensive drug in the general treatment regimen.

Additionally, as per the other studies, it was difficult to ascertain the percentage and prevalence of the hearing loss identified. From the results of the 15 that were present for more than the baseline; 100% showed ototoxicity in DPOAEs, 93% showed ototoxicity with TUNE and ASHA, and 7% with CTCAE. This is in accordance with other studies which shows about 7-90% (Peterson and Rogers, 2015). Nevertheless, it is unclear as to which description should be used.

Also, the results seem to fluctuate between the weeks, and so hearing aid fitting may be questionable during treatment, and perhaps should be considered post-treatment. This does not take the psycho-social factors into account. As the most significant changes in the hearing were noted in weeks 2 and 6 with PTA, these weeks are suggested to be incorporated in a DR-TB monitoring protocol, where testing every one to two weeks may not be possible in a low resource setting.

9.1.2. Pharmacokinetics of kanamycin and capreomycin

In summary, the pharmacokinetics yielded erratic results, mostly within the peak levels, particularly with kanamycin. The capreomycin target range is between 20 μg/ml and 40 μg/ml, yet the mean peak was 8.1 μg/ml. The kanamycin target peak is between 20μg/ml and 35 μg/ml, and the mean peak levels found were at 20 μg/ml, yet with a large SD of ±16.5.

The average peak levels of kanamycin ranged, but on average were within the therapeutic range, where the capreomycin peak levels appeared sub-therapeutic. For both kanamycin and capreomycin, the trough levels were always below 10 μg/ml and not within a toxic range. The pharmacokinetics of were not as expected. The peak levels of kanamycin in some instances and capreomycin were subtherapeutic, which does not correlate to literature.

Furthermore, average CrCl was reduced for those taking kanamycin, yet majority was within the normal range for capreomycin. This is in accordance with literature; capreomycin is not as toxic as kanamycin, and thus less nephrotoxicity in these patients was noted.

Additionally, despite the low peak levels, all participants that could be documented culture converted within the first two months. However, this included one negative culture, in comparison to the standard two consecutive cultures. This was not as expected, however low peak levels with positive treatment outcomes has been observed in another study (Namazi et al., 2016). Furthermore, the Resuscitation-promoting factors may also provide an explanation for these seemingly positive outcomes. However, this theory is only based on preliminary and animal results.

9.1.3. Pharmacokinetics and Hearing Levels

It can be concluded that no correlation was observed with trough levels and ototoxicity. The pharmacokinetic results were erratic and differed considerably between individuals. A conclusive positive or negative relationship between dosage and trough levels was not observed with the progression of hearing loss.

Furthermore, in some instances, when looking at mean levels, dosage did correlate to ototoxicity, yet when looking at individual patients, dosage did not correlate to ototoxicity. The dose per kg throughout the weeks for kanamycin remained stable, and cannot be correlated to the change in hearing yet the dose per kg of capreomycin at week 10 and 12 was

the highest, and the most significant change in hearing was noted. This is likely due to the fact of accumulation over time and not necessarily the dose per kilogram.

Further studies with larger sample size and UHFA are needed to ascertain the exact relationship between pharmacokinetics and hearing levels.

9.1.4. Feasibility Findings

The overall aim of this study was to establish the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship of these medications with hearing levels.

Various hurdles were identified that affected the feasibility; particularly participant factors such as willingness to participate, enrolment and attrition as well as data related issues, specifically with the blood sampling, both for pharmacokinetics and creatinine levels.

Participation in the study was a significant factor. In summary, of a potential 268 participants at both hospitals, only 22 were enrolled after 12 months of recruitment. This poor enrolment and retention were f a variety of reasons; from a willingness to participate, social and emotional difficulties, as well as the exclusion based on inclusion and exclusion criteria. Furthermore, resources were limited to continue the study for a more extended period and to improve the sample size potentially.

Blood sampling issues arose from destroyed samples for kanamycin and capreomycin analysis, mainly from haemolysis. Furthermore, many of the creatinine levels could not be found on the NHLS website, despite the samples being drawn. The reason for this is unknown.

Despite the low peak and trough levels with kanamycin and capreomycin, changes in hearing were noted (more so for kanamycin than capreomycin), as well as reduced CrCl levels with the kanamycin patients. Therefore, toxicity was noted. Lastly, despite the sub-therapeutic peak levels, patients culture converted within the first two months of treatment.

Therefore, with the small sample size achieved, as well as erratic levels with regards to the pharmacokinetics, substantial issues with regards to the feasibility of more extensive studies were identified. These issues, such as willingness to participate, blood sampling issues, large variations with results, quality assurance, resources available in this low resource setting, variations between treatment sites as well protocol variations between institutions need to be considered to conduct a more substantial, yet necessary study. Based on the results achieved, it would not be feasible to perform TDM for kanamycin and capreomycin to reduce ototoxicity, and further investigations need to be conducted.

9.2. Strengths of the Study

The study portrayed various strengths which will be described. This study was unique as it was the first study as such. It also led to the development of an ototoxicity monitoring protocol specific for the population, together with the mobile application. Further, it displayed the feasibility of conducting more extensive studies, by depicting the 'real life' situation.

9.2.1. First of its kind

This study incorporating the pharmacokinetics and correlating them to hearing loss, for both kanamycin and capreomycin was the first of its kind. At present, when ototoxicity is noted, the injectables are often reduced to three days a week, with no pharmacokinetic measurements. This study created awareness to the possible adverse outcomes of this method (such as low peak levels which may impact treatment outcomes).

9.2.2. Ototoxicity Monitoring Protocol

This study identified the need for a standardised comprehensive monitoring program, specifically for the DR-TB population. Therefore, a recommended monitoring protocol was devised, together with a mobile application, taking ultra-high frequencies into account.

It also brought to light the need for interdisciplinary monitoring and management within this population in ensure optimal outcomes. It is vital for doctors, nurses, pharmacists and audiologists to understand the basics of each scope in order to work together collaboratively and respectfully.

This study also highlighted the possibility of nursing staff to implement the ototoxicity monitoring protocol when trained appropriately. At present, nurses are implementing some type monitoring with no training and understanding. This study shows that with the correct training outcomes can be reliable.

9.2.3. Development of an ototoxicity calculator mobile application

Throughout the study, the need for a standardised and user-friendly method to interpret hearing results was identified. It was evident that doctors, audiologists and nurses experienced difficulty in identifying a significant hearing loss and the need for dosage adjustments based on these audiologic results. Therefore, as an outcome of the study, an ototoxicity monitoring protocol for DR-TB and mobile ototoxicity calculator application, ‘otocalc’, was developed. ‘OtoCalc” assists healthcare workers with the calculation of a significant hearing loss, its equivalent grade and recommendations for management.

However, this newly developed application needs to be trialled by various health care professionals, such as doctors, nurses, pharmacists and audiologists within the DR-TB

population. Hopefully, it will standardise treatment and allow for reliable statistics and follow-up of the patients on a single database throughout the country.

9.2.4. Data collection portrayed the feasibility of a more extensive study by depicting a 'real life' clinical situation

This study, although had many weaknesses, particularly the poor enrolment and high dropout, however, it also highlights the extent of the problem with patient follow up and continuation of follow through of treatment.

9.3. Limitations of the Study

9.3.1. Sample Size Limitation

The small sample size limited the ability to generalise the findings and the inclusion of the covariables in the analysis. Nevertheless, it did depict the challenges we are faced with when treating this population and conducting research.

Also, many of these patients started on kanamycin, were switched to capreomycin, and thus it is difficult to ascertain which drug was more ototoxic. Also, those that were showing ototoxicity were switched to capreomycin. It is likely that these specific patients had the gene for ototoxicity, and thus their loss of hearing at the end was an indication of the gene and not general toxicity of the capreomycin or pharmacokinetic factors.

Although the data that was hoped for was not all obtained, other evidence came to light such as the difficulties treating this population, and the problems we are facing with the decentralisation of treatment.

Furthermore, due to the small sample size, covariables could not be included in the analysis. Initially, at the development of the protocol, when the sample size was calculated at 80 participants, the researcher aimed to include various subgroups and covariates (e.g. age,

gender, HIV, ARV, BMI, concomitant medications, frequency of kanamycin/capreomycin dosing, and difference in the protocol at the research sites) in the analysis. However, based on the sample size achieved in the current study, this analysis was not possible. The subgroups and covariable included:

9.3.2. Data Limitations

There were various shortfalls in the data collection, resulting in limitations with the outcomes. Shortfalls included the loss of various pharmacokinetic blood samples, as well as the inability to access some of the creatinine measurements from the NHLS database.

Furthermore, the multisite aspect of this study, although unavoidable at the time, did create variability which was not ideal. The two sites had different treating doctors, slightly different protocols, as well as different drugs available, which created hurdles when interpreting the data.

Additionally, at times, various data were not collected as planned. This included the DPOAE measurements with poor SNR ratios, the study coordinator not measuring the height of participants at all times, and so BMI could not be analysed, as well as difficulties with the transportation of the blood. The study coordinator reportedly planned to use the measurements from the hospital files, so as not to inconvenience the participant by measuring it twice. However, when completing this part of the case report forms, it could not be found in the hospital files.

Also, although the cultures converted for those participants where results were available, the long-term results were not traced. As thus it was not possible to identify if those participants were cured for the long term, which could correlate to the low peak levels. Ideally, future studies should investigate the long-term results in correlation to the pharmacokinetics.

9.3.2.1. Change in Policy

As the time of the data collection, the NDoH published guidelines introducing then new drugs, such as linezolid and bedaquiline. HJH, being a research site, was one of the sites that implemented the use of these drugs, specifically bedaqualine. Despite these new guidelines, the new drugs are costly, and the aminoglycosides and capreomycin are still being used, and consequently, the outcomes of this current study are still relevant.

9.3.3. Implications of the Study

9.3.3.1. Clinical implications – audiology.

Hearing loss can affect ones' quality of life by affecting the ability to communicate. This hindered, or lack of communication can affect socialisation, professional opportunities,

Additionally, hearing aids are expensive items, well over R2500.00 each for a basic hearing device. As so many individuals are infected with DR-TB in South Africa, it is likely that these individuals will require hearing aids post-treatment, which correspondingly places enormous financial pressure on the government's health department; a department already suffering the burdens of a developing country. Hearing aids are not a 'once off' cost, as they require maintenance including hearing aid repairs, new ear moulds, replacements batteries, and new hearing aids every few years as they do not last a lifetime. Audiologists are also needed to conduct the hearing evaluations, hearing aid fittings, aural rehabilitation and ongoing assistance. Thus, the expense and burden of the government to provide these services is tremendous.

Hearing loss can also further result in emotional and social difficulties, including loneliness, decreased self-esteem and various other difficulties (Wallhagen, Strawbridge, Cohen & Kaplan, 1997). This can impact on an individual's ability to function and obtain work. Severe depression can become a comorbid disability, resulting in the need for further

disability grants; again, placing financial burdens on the country. This individual's mental state also impacts on his/her family, and their entire units' wellbeing.

Clinically, a comprehensive audiology monitoring program (as outlined in Chapter 8) must be included in practice, with standardised criteria for grading hearing loss and its implications for management. The counselling is imperative as well in order to ameliorate the impact on quality of life. The 'ototcalc' application can also assist with this management.

In summary, the government needs to ensure adequate resources (financial and personnel) for the implementation and maintenance of an ototoxicity monitoring programme and aural rehabilitation.

9.3.3.2. Clinical implications – pharmacokinetics.

Pharmacotherapy-induced ototoxicity is growing, especially in developing countries such as South Africa, where often, more expensive and less toxic drugs are unavailable to the majority of the population. This highlights the importance of ototoxicity monitoring and management of hearing loss. Due to the nature of the hearing loss, resulting from pharmacotherapy, the necessity for interdisciplinary teamwork between the audiologist, pharmacist, medical doctor and nursing staff in the wards results in best practice and management of patients with ototoxic damage, with the inclusion of pharmacokinetic measurements (Schellack, Wium, Ehlert, van Aswegan & Gous, 2015). At present, the interdisciplinary aspect is not being carried out in many institutions and outpatient clinics. However, due to the multi-faceted nature of ototoxicity, it is clearly a necessity for interdisciplinary care. Further training of these professionals through universities and continuing professional development (CPD) courses is essential. However, the protocol and 'Otocalc' would assist with this aspect.

9.3.3.3. Research implications – audiology and pharmacokinetics.

The identification of this hearing loss, as well as deeper understanding of the hearing loss in relation to the injectable pharmacokinetics, is an important step to alleviate or manage the hearing loss. Although this study did not yield a causative relationship of trough levels and hearing loss, it brings forth the possibility of other factors and drugs that may be contributing to hearing loss, which can perhaps be explored further.

Also, in recent years, the possibility of new drugs has come to life, such as bedaquiline and linezolid, as well as a shorter duration of the injectable regimen. These drugs and new regimen can add immense improvements to the DR-TB treatment program. However, as with most drugs, side effects are inevitable, and bedaquiline and linezolid have their own side effects. Therefore, even with the positive additions of new drugs and shorter regimens, there will still be the need for aminoglycosides in some instances; although hopefully in a much smaller population.

Moreover, the full understanding of their pharmacokinetics, side effects and outcomes in aminoglycosides is of utmost importance as, despite new drugs, aminoglycosides will likely be used in this population. This current study assisted with the understanding of this ototoxic hearing loss from aminoglycosides, which will be investigated further in an upcoming study. The study will be done with a larger sample, and the newly developed protocol and mobile application.

9.3.3.4. Policy implications.

Public health aspects need to be considered when treating DR-TB; not purely the scientific aspects such as pharmacokinetics, and side effects such as toxicity (nephrotoxicity and ototoxicity). van Rie and Enarson (2006) discuss that treating DR-TB is feasible and can be effective, even in low-income countries. However, this plan must be based on sound

public-health practice including good laboratory infrastructure, appropriate treatment regimens, proper management of side-effects, and sufficient resources to maintain adherence and prevent further resistance. In summary, the management is a public health problem, where all parameters must be treated together to stop the spread of the disease and further resistance. This was a prominent finding in this study, showing the poor infrastructure and retention of patients in the treatment program. Therefore, in addition to investigating and understanding the pharmacokinetics of the injectable as well as the adverse events of the treatment, this study suggested the need for a better overall public health system.

The implications further extend into ototoxicity monitoring methods of patients with DR-TB. As there is currently no standard protocol to monitor ototoxicity in patients with DR-TB, this research proposed a protocol as well as a mobile application in terms of a calculator to assist in this process. This calculator and method will further identify the specifics of hearing loss, in order to understand its type, configuration, progression and symmetry to allow for further relationships with drug properties as well as other individual factors to be drawn. This study also introduced the possibility of utilising nurses to implement ototoxicity monitoring programs, yet only when appropriately and adequately trained. As our country does not have enough audiologists to implement ototoxicity monitoring programs, thus nurses can possibly assist with reducing this burden from audiologists. The possibility of nurses conducting the testing can be further be explored, as this study presented the feasibility.

9.4. Recommendations for future research

9.4.1. Larger Sample Size and Inclusion of Covariables

A study further investigating the pharmacokinetics of kanamycin and capreomycin as well as the relationship to hearing in a more substantial sample size is recommended. This

will allow for more conclusive evidence to be drawn including the generalisation of the results, as well as the analysis of possible covariables and subgroups to be examined.

9.4.2. Audiological Recommendations:

9.4.2.1. Ototoxicity monitoring program and use of 'otocalc' in South Africa.

This study proposed the use of a standardised ototoxicity monitoring protocol, as well as developed a mobile application to standardise the identification and classification of hearing loss. In order for this to be incorporated into guidelines, further research must be conducted. The proposed ototoxicity monitoring protocol and the Otocalc application will be piloted at one of the research sites in 2018.

9.4.2.2. DPOAEs.

Screening with DPOAEs may be enhanced by testing only in the 3- to the 5.2-kHz range, thus decreasing testing time. Higher time averages to increase the signal-to-noise ratio and use of this narrower bandwidth might also allow for accurate bedside testing (Ress et al., 1999). However, more research needs to be done with regards to specific frequencies for testing. This study showed ototoxicity was detected from 2 kHz. However, higher frequency testing is more sensitive. Moreover, DPOAEs are quick to run, 2 to 12 kHz is recommended until more supporting evidence can be found with a shorter protocol.

The grading system recommended does not take DPOAEs into account. However, further research is needed to correlate the DPOAEs to the PTA, and make recommendations on significant results to motivate for dosage changes.

9.4.2.3. Ultra-High Frequency normative values.

It is questioned whether a general standard for hearing levels is meaningful at all and that normative data for various age groups should instead be used as a reference level (Osterhammel & Osterhammel, 1978). However, based on this study, grades in the higher

frequencies were prescribed to assist in guiding treatment. Nevertheless, it would be useful to obtain normative data for the ultra-high frequencies, and thus the grading system may need to be adjusted over time.

9.4.2.4. Otoprotection.

Various otoprotective methods have been studied for quite some time now (Campbell, 2004). Otoprotective agents may be a useful method of preventing hearing loss in patients treated with lifesaving aminoglycosides (Campbell, 2004). Further investigations of the safety and efficacy of otoprotective agents such as D-methionine and N-Acetylcysteine should be investigated in this population (Campbell, 2004; Atkuri, Mantovani, Herzenberg & Herzenberg, 2007).

9.4.3. Pharmacological Recommendations

Further studies with larger samples are recommended to establish the pharmacokinetics of kanamycin and capreomycin in this population. Also, it is recommended that the long-term outcomes, specifically culture conversion and possible relapse be investigated in relation to the pharmacokinetics and pharmacodynamics.

9.5. Conclusion

Poor TB diagnostic and treatment coverage globally, social and economic instability in many high-burden countries and the presumed increasing transmission of drug-resistant strains are making the battle against drug-resistant TB one of the most important and relevant health challenges of the 21st century (Günther, 2014). This is only increasing the prevalence of hearing loss globally, particularly in South Africa. Hearing loss cannot and must not continue to be a silent epidemic (Editorial, the Lancet, 2016). Helen Keller once said, "*Deafness separates people from people*" (Sherman, 1997). Hearing loss can have profound

effects not only on interpersonal communication, but also on health, independence, well-being, quality of life, and daily function. Although this hearing loss receives limited research funding and public awareness. Global multidisciplinary and collaborative efforts are urgently needed to address the health needs of the child and adult with hearing loss (Editorial, the Lancet, 2016).

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Appendices

Appendix A

Initial Ethics Approval Letter

Subsequent Ethics Approval Letter (with amendments)

Final Ethics Approval Letter (with amendments)

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Ms V Graham

Regulatory Manager
Clinical HIV Research Unit
Helen Joseph Hospital, Themba Lethu Clinic
Perth Road, Westdene
2092

Fax: 011 276 8820

FAXED & COURIE

30 January 2015

Dear Ms Graham,

PROTOCOL: KANAMYCIN STUDY - A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS OF KANAMYCIN IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND THE RELATIONSHIP BETWEEN THERAPEUTIC DRUG MONITORING AND HEARING LEVELS

ETHICS REFERENCE NO: 141104

RE : APPROVAL FOR AMENDMENTS TO KANAMYCIN PROTOCOL

We acknowledge receipt of your letter dated 05 December 2014 with the following documentation pertaining to the above-captioned trial.

Amendment Date:	04-Dec-14	Amendment Version:	Version 1.3
Amendment Number:		Received Date:	05-Dec-14

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Protocol: Kanamycin Study Version 1.3 dated 04/12/214
* Appendices, Version 1.3: 04/12/2014:

- Appendix A which includes:
  Eligibility Consent Form and HIV Testing Consent Form
  HIV Counselling Form - PART A: Patient Demographics and Social Information
  HIV Counselling Form - PART B: Pre-Test Counselling
  HIV Counselling Form - PART C: Post-Test Counselling
  HIV Counselling Form - PART D: Adherence Counselling

- Appendix B: Referral Document/Eligibility Checklist
- Appendix C: Inclusion and Exclusion Criteria
- Appendix D: Signing of an informed consent document as per GCP guidelines
- Appendix E: Information Leaflet and Informed Consent for participation in the study
- Appendix F: Participant Information and Case History Form
- Appendix G: Baseline Audiological Measures
- Appendix H: Blood Sample Form
- Appendix I: Pharmacokinetic Data Form
- Appendix J: Participant Case Report Form
- Appendix K: Kanamycin Drug Diary
- Appendix L: Financial Agreement with Participant
- Appendix M: Blood Storage and Transportation
- Appendix N: Confirmation that Participant has Received Remuneration
- Appendix O: Flow Chart
- Appendix P: Activity Checklists

Noted and approved:
Following the corrections from the HREC (sent in on 04 December 2014), the site would like to request 2 amendments to the protocol:
1. Request to add another study visit (on day 3)
2. Request to adjust daily transport money

Request 1
The study protocol had 8 scheduled study visits (day 1, 2, 15, 28, 40, 54, 68, 84). The site would like to add in a 9th study visit on day 3.

'We need to obtain baseline pharmacokinetic measurements of the kanamycin. The first dose of kanamycin is given on day 2, and then blood is drawn 4 to 6 hours later. This will allow the measurement of the peak levels, but not the trough level. We therefore need the participants to return on day 3 in order to draw blood 30 to 60 minutes before the second dose of kanamycin, in order to obtain the trough levels.

This has been adapted in the informed consent. We are not drawing more blood in total, as originally we were going to draw the trough on day 2. However, this was an error as we cannot do this. Therefore the same amount of blood will be drawn, just at a different time interval.'

This has been adjusted in the Appendices:
* Informed consent (pages 16 and 17)
* Flow Chart (page 47)
* Study Checklist (pages 50 and 51)
* Protocol (page 22)

Request 2
The site would like to request an adjustment in daily participant transport money.

'In the previous protocols (version 1.1 and 1.2), participants were to receive:
* R150 for the study visits (8 in total over the 3 months). On these days, they will need to be at the clinic for longer time periods for the study related procedures, such as hearing and/or blood tests.
* R100 daily transport money to come to the clinic to receive their kanamycin injection and dosage adjustment (no blood or hearing tests).

However, the budget is extremely limited. We have added in another study visit (the 9th visit as above). Participants will need to receive R150 for these visits as there is a study procedure and blood will be drawn.

However, we would like to request an adjustment in the R100 transport money for the daily visits, and adjust the amount on an individual basis, depending on the areas that the participants live.

Therefore, we will provide them with enough money for their transport, however, the participants who comes from areas such as Germiston will receive R100 (or more if this does not cover the fee), and the participants from areas such as Westdene will receive less than R100. We hope this will allow this to fit better in the limited budget, as unfortunately, we have very limited funds.'

These amendments have been made to the Appendices:
* Informed consent (page 19)
* Financial Agreement (page 41)
* Confirmation that participant has received the money (page 45)
* Study checklist (page 51)

Noted:
'We kindly request for this to be reviewed as soon as possible, to allow us to enroll participants from January 2015. We are aware that this is a special request, and may not be easy, but would greatly appreciate it if you would be able to assist. The study budget is allocated for 1 calendar year only, beginning in January 2015, and thus we if possible, we would very much appreciate it if we could do so.'

Ethics Approval Date: 30 January 2015

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

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* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

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* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Dr MS Rassool,

Clinical HIV Research Unit
Helen Joseph Hospital
Perth Road, Westdene
Johannesburg
2041

Fax: 011 482 2130

FAXED & COURIE

30 January 2015

Dear Dr Rassool,

PROTOCOL: KANAMYCIN STUDY - A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS OF KANAMYCIN IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND THE RELATIONSHIP BETWEEN THERAPEUTIC DRUG MONITORING AND HEARING LEVELS

ETHICS REFERENCE NO: 141104

RE : APPROVAL FOR AMENDMENTS TO KANAMYCIN PROTOCOL

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Amendment Number:		Received Date:	05-Dec-14

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* Protocol: Kanamycin Study Version 1.3 dated 04/12/214
* Appendices, Version 1.3: 04/12/2014:

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- Appendix N: Confirmation that Participant has Received Remuneration
- Appendix O: Flow Chart
- Appendix P: Activity Checklists

Noted and approved:
Following the corrections from the HREC (sent in on 04 December 2014), the site would like to request 2 amendments to the protocol:
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2. Request to adjust daily transport money

Request 1
The study protocol had 8 scheduled study visits (day 1, 2, 15, 28, 40, 54, 68, 84). The site would

like to add in a 9th study visit on day 3.

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* R100 daily transport money to come to the clinic to receive their kanamycin injection and dosage adjustment (no blood or hearing tests).

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'We kindly request for this to be reviewed as soon as possible, to allow us to enroll participants from January 2015. We are aware that this is a special request, and may not be easy, but would greatly appreciate it if you would be able to assist. The study budget is allocated for 1 calendar year only, beginning in January 2015, and thus we if possible, we would very much appreciate it if we could do so.'

Ethics Approval Date: 30 January 2015

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1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

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* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).

- Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

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* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

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* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

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As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES
For and on behalf of the Human Research Ethics Committee: (Medical)

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Ms V Graham

Regulatory Manager
Clinical HIV Research Unit
Helen Joseph Hospital, Themba Lethu Clinic
Perth Road, Westdene
2092

Fax: 011 276 8820

FAXED & COURIE

07 April 2015

Dear Ms Graham,

PROTOCOL: KANAMYCIN STUDY - A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS OF KANAMYCIN IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND THE RELATIONSHIP BETWEEN THERAPEUTIC DRUG MONITORING AND HEARING LEVELS

ETHICS REFERENCE NO: 141104

RE : APPROVAL FOR AMENDMENTS TO KANAMYCIN PROTOCOL

We acknowledge receipt of your letter dated 25 March 2015 with the following documentation pertaining to the above-captioned trial.

Amendment Date:		Amendment Version:	Version 1.4
Amendment Number:		Received Date:	25-Mar-15

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Information Leaflet and Informed Consent for participation in the study, Version 1.4

Noted and approved:

'Following the amendments to the HREC (30 January 2015) and subsequently the translated informed consents sent in March 2015, we would like to request 4 amendments to the participant information booklet and informed consent document as well as to add another appendix (drug diary) please:

Informed Consent Changes:

1. Logistical move - Request to move the daily clinic visit from Helen Joseph TB focal point to the participants' local clinic.
2. Request to adjust daily transport money for the local clinic visits
3. Layout changes – page numbers added
4. Version changed to version 1.4

Appendix:

5. Request to add daily drug diary for local clinic sister

Request 1
Logistical move - Request to move the daily clinic visit from Helen Joseph TB focal point to the participants' local clinic
At the moment, participants are required to come to the Helen Joseph Clinic daily for their kanamycin injections. We originally decided to do this for quality control – to ensure that all participants can be monitored daily and correct dosages are given and recorded.

However, the study has been officially 'running' for 5 weeks, and we only have 3 participants, who are not

compliant with coming daily. Many participants are not willing to commit to come daily, despite being provided with transport money. The participants who have consented are proving too ill to travel daily to the clinic.

And so, we would like to amend the protocol and informed consent to allow for the participants to receive their kanamycin injections and directly observed treatment at their local clinic.
However, for quality control purposes, the study nurses will liaise closely with the clinic nurses for 'buy in'; to ensure the injections are carried out reliably. The study coordinators and nurses will follow up consistently with the clinic sisters and consistent communication will assist in maintaining quality and reliability of the injections and dosage adjustments.

Participants will still be required to come to Helen Joseph Hospital for the hearing and blood tests every 2 weeks (baseline, week 2, 4, 6, 8, 10 and 12). Participants in the experimental group will be required to come in additionally for their dosages adjustments and to receive their new script from the doctor. This will take place on weeks 1, 3, 5, 7, 9 and 11.

This has been adjusted in the informed consent booklet on pages 2, 3, 4, 9 and 14 (highlighted in yellow).

Request 2
Request to adjust daily transport money for the local clinic visits
As per the previous protocol, R70 was agreed to be paid for daily transport to Helen Joseph Hospital for the kanamycin injections, while R150 would be paid for transport and food for study visits whereby hearing and blood tests were done.

The blood and hearing tests can take approximately 6 hours (as we are required to wait approximately 6 hours between the two blood tests- peak and trough), and so the R150 would
also compensate for a day of work.

However, R70 was chosen for daily visits because the participants were only required to come for a short amount of time for their injection, and so this was required to cover transport. If this was not sufficient though, it could be discussed, and allowance would be made.

However, we request to adjust the transport money once again for the daily visits to the local clinics. The local clinics are generally closer than Helen Joseph clinic, and so less transport money would be required, and so we request to drop the transport money to R50 for the daily trips to the local clinic. However, should the participant wish to come to Helen Joseph for their daily injections, they will be given the option, and will then be provided with the R70 for more transport money. When the experimental group is required to visit Helen Joseph Hospital for a new script, R70 will be provided on this day, as this is a quick visit, but more transport money would be needed that to their local clinic.

These amendments have been made to the informed consent on pages 3 and 9 (highlighted in yellow) where finance is discussed.

Request 3
Layout changes – page numbers added
Page numbers were added in the informed consent to ensure that no pages go missing and thus for quality assurance purposes.

Request 4
Version changed to version 1.4
The previous informed consent was version 1.3, and so this has been updated to 1.4.

Please see pages 1 and 14 (highlighted in yellow) in the informed consent.

Request 5
Request to add daily drug diary for local clinic sister

As per the protocol, the study coordinator is required to document the date, time and dosage of the injection as well as of the other medications and dosages administered.

We would now need the local clinic sister to assist in providing us with this information.

We therefore have drawn up a 'drug diary' which will allow ease of use for the clinic sister. The standard oral TB medications are prescribed at Helen Joseph Hospital, and so these dosages will be recorded in the study file. The study nurse will therefore be required to directly observe the treatment, administer and record the injection, and documents any other medications. This will assist in the quality of the study.

The 'drug diary' has been attached.

We kindly request for these amendments to be reviewed as soon as possible in order to allow us to enroll

more participants as soon as possible. The study budget is allocated for 1 calendar year only, which began in January 2015, and thus we if possible, we would very much appreciate it if we could increase our study participant numbers with the above changes as soon as possible.'

Ethics Approval Date: 07 April 2015

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

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1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

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.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

.

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Dr MS Rassool,

FAXED & COURIE

07 April 2015

Clinical HIV Research Unit
Helen Joseph Hospital
Perth Road, Westdene
Johannesburg
2041

Fax: 011 482 2130

Dear Dr Rassool,

PROTOCOL: KANAMYCIN STUDY - A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS OF KANAMYCIN IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND THE RELATIONSHIP BETWEEN THERAPEUTIC DRUG MONITORING AND HEARING LEVELS

ETHICS REFERENCE NO: 141104

RE : APPROVAL FOR AMENDMENTS TO KANAMYCIN PROTOCOL

We acknowledge receipt of your letter dated 25 March 2015 with the following documentation pertaining to the above-captioned trial.

Amendment Date:		Amendment Version:	Version 1.4
Amendment Number:		Received Date:	25-Mar-15

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Information Leaflet and Informed Consent for participation in the study, Version 1.4

Noted and approved:

'Following the amendments to the HREC (30 January 2015) and subsequently the translated informed consents sent in March 2015, we would like to request 4 amendments to the participant information booklet and informed consent document as well as to add another appendix (drug diary) please:

Informed Consent Changes:

1. Logistical move - Request to move the daily clinic visit from Helen Joseph TB focal point to the participants' local clinic.
2. Request to adjust daily transport money for the local clinic visits
3. Layout changes – page numbers added
4. Version changed to version 1.4

Appendix:

5. Request to add daily drug diary for local clinic sister

Request 1
Logistical move - Request to move the daily clinic visit from Helen Joseph TB focal point to the participants' local clinic
At the moment, participants are required to come to the Helen Joseph Clinic daily for their kanamycin injections. We originally decided to do this for quality control – to ensure that all participants can be monitored daily and correct dosages are given and recorded.

However, the study has been officially 'running' for 5 weeks, and we only have 3 participants, who are not compliant with coming daily. Many participants are not willing to commit to come daily, despite being provided with transport money. The participants who have consented are proving too ill to travel daily to the clinic.

And so, we would like to amend the protocol and informed consent to allow for the participants to receive their kanamycin injections and directly observed treatment at their local clinic.
However, for quality control purposes, the study nurses will liaise closely with the clinic nurses for 'buy in'; to ensure the injections are carried out reliably. The study coordinators and nurses will follow up consistently with the clinic sisters and consistent communication will assist in maintaining quality and reliability of the injections and dosage adjustments.

Participants will still be required to come to Helen Joseph Hospital for the hearing and blood tests every 2 weeks (baseline, week 2, 4, 6, 8, 10 and 12). Participants in the experimental group will be required to come in additionally for their dosages adjustments and to receive their new script from the doctor. This will take place on weeks 1, 3, 5, 7, 9 and 11.

This has been adjusted in the informed consent booklet on pages 2, 3, 4, 9 and 14 (highlighted in yellow).

Request 2
Request to adjust daily transport money for the local clinic visits
As per the previous protocol, R70 was agreed to be paid for daily transport to Helen Joseph Hospital for the kanamycin injections, while R150 would be paid for transport and food for study visits whereby hearing and blood tests were done.

The blood and hearing tests can take approximately 6 hours (as we are required to wait approximately 6 hours between the two blood tests- peak and trough), and so the R150 would
also compensate for a day of work.

However, R70 was chosen for daily visits because the participants were only required to come for a short amount of time for their injection, and so this was required to cover transport. If this was not sufficient though, it could be discussed, and allowance would be made.

However, we request to adjust the transport money once again for the daily visits to the local clinics. The local clinics are generally closer than Helen Joseph clinic, and so less transport money would be required, and so we request to drop the transport money to R50 for the daily trips to the local clinic. However, should the participant wish to come to Helen Joseph for their daily injections, they will be given the option, and will then be provided with the R70 for more transport money. When the experimental group is required to visit Helen Joseph Hospital for a new script, R70 will be provided on this day, as this is a quick visit, but more transport money would be needed that to their local clinic.

These amendments have been made to the informed consent on pages 3 and 9 (highlighted in yellow) where finance is discussed.

Request 3
Layout changes – page numbers added
Page numbers were added in the informed consent to ensure that no pages go missing and thus for quality assurance purposes.

Request 4
Version changed to version 1.4
The previous informed consent was version 1.3, and so this has been updated to 1.4.

Please see pages 1 and 14 (highlighted in yellow) in the informed consent.

Request 5
Request to add daily drug diary for local clinic sister

As per the protocol, the study coordinator is required to document the date, time and dosage of the injection as well as of the other medications and dosages administered.

We would now need the local clinic sister to assist in providing us with this information.

We therefore have drawn up a 'drug diary' which will allow ease of use for the clinic sister. The standard oral TB medications are prescribed at Helen Joseph Hospital, and so these dosages will be recorded in the study file. The study nurse will therefore be required to directly observe the treatment, administer and record the injection, and documents any other medications. This will assist in the quality of the study.

The 'drug diary' has been attached.

We kindly request for these amendments to be reviewed as soon as possible in order to allow us to enroll more participants as soon as possible. The study budget is allocated for 1 calendar year only, which began in January 2015, and thus we if possible, we would very much appreciate it if we could increase our study participant numbers with the above changes as soon as possible.'

Ethics Approval Date: 07 April 2015

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

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8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

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The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES
For and on behalf of the Human Research Ethics Committee: (Medical)

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- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to PO_HEC-001 and SOP-HEC-008, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study.

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reasons stated.

* The investigators authorised by this approval participate in this study. Additional investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

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* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

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6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

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As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will redo courses completed by investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator (s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
[illegible]

[illegible]

Ms C. Hollander, [illegible]

Clinical HIV Research Unit (CHRU) 31 July 2017
Helen Joseph Hospital
[illegible]

Fax: [illegible]

Dear Ms Hollander,

[illegible]

ETHICS REFERENCE NO: [illegible]

[illegible]

[illegible]

Amendment Date:	17-Jul-2017	Amendment Version:	Version 1.0
Amendment Number:		Received Date:	19-Jul-2017

The following has been approved by the Wits Human Research Ethics Committee (Medical):

* Protocol: Kanamycin Study Version 1.0 dated 17 July 2017

The content of the cover letter has been noted and approved.

Ethics Approval Date: 31 July 2017

[illegible]

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* [illegible]

* [illegible]

* [illegible]
  - [illegible]
  - [illegible]

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x3039, Houghton 2041, South Africa Tel: +27-11-214 6206 Fax: +27-11-214 6391

Ms V Graham

FAXED & COURIERED

25 May 2015

Regulatory Manager
Clinical HIV Research Unit
Helen Joseph Hospital, Themba Lethu Clinic
Perth Road, Westdene
2092

Fax: 011 276 6820

Dear Ms Graham,

PROTOCOL: KANAMYCIN STUDY - A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS AND PHARMACODYNAMICS OF KANAMYCIN AND CAPREOMYCIN IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS AND THE RELATIONSHIP BETWEEN HEARING LEVELS

ETHICS REFERENCE NO: 141134

RE : APPROVAL FOR AMENDMENTS TO KANAMYCIN PROTOCOL

We acknowledge receipt of your letter dated 21 May 2015 with the following documentation pertaining to the above-captioned trial.

Amendment Date:	21-May-15	Amendment Version:	Version 1.5
Amendment Number:		Received Date:	21-May-15

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Protocol: Kanamycin Study Version 1.5 dated 21 May 2015
* Screening Consent Form, Version 1.5
* Informed Consent - Helen Joseph Hospital, Version 1.5
* Informed Consent - South Rand Hospital, Version 1.5
* Study Checklist, Version 1.5 dated 18 May 2015

The following request is approved subject to receipt of the Hospital CEO permission:
* Additional Site: South Rand Hospital, Friars Hill Road, Johannesburg South, 2197

Ethics Approval Date: 25 May 2015

This University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

Appendix B

Letter of Permission from Helen Joseph Hospital

Letter of Permission from South Rand Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
Chief Executive Officer
Tel: (011) 489-0306/1087
Fax: (011)726-5425
Email:Raymond.Billa@gauteng.gov.za

PERMISSION TO CONDUCT RESEARCH AT HELEN JOSEPH HOSPITAL

PRINCIPAL RESEARCHER

FULL NAME

Dr. Mohammed Rassool

DESIGNATION

Senior Medical Officer - Clinical HIV Research Unit Wits Health Consortium

CONTACT NUMBER

Tel: +27 11 276-8800 / Direct: +27 11 276-8813 / Mobile: +27 83 415 8967

E-MAIL ADDRESS

mrassool@witshealth.co.za

DEPARTMENT

Department of Medicine, University of Witwatersrand Helen Joseph Hospital, Themba Lethu Clinic

HEAD/S OF DEPARTMENT/S

Prof. I.M Sanne

TITLE OF RESEARCH

A FEASIBILITY STUDY INVESTIGATING THE PHARMACOKINETICS OF KANAMYCIN IN PATIENTS WITH DR-TB AND THE RELATIONSHIP BETWEEN THERAPEUTIC DRUG MONITORING AND HEARING LEVELS

OBJECTIVES OF RESEARCH

OVERALL AIM:

The aim of this study will serve as a feasibility study to investigate the otoprotective effects of TDM using audiological and pharmacological measures in patients treated with KM for DR-TB

PRIMARY AIMS:

1. The primary objective is to compare the proportion of patients in each study arm who experience clinically significant hearing loss during the study (as different from baseline measurement), using PTA testing.

2. To examine the relationship between KM dosing and hearing levels
   - 2.1. To explore the relationship between KM dosing and the progression of hearing loss
   - 2.2. To explore the relationship between KM dosing and the degree of hearing loss

SECONDARY AIMS

3. To investigate whether Therapeutic Drug Monitoring (TDM) affects KM dosing?
   - 3.1. To examine whether TDM affects the average dose of KM per kilogram
   - 3.2. To establish the number of dosage changes of KM in the first 3 months of treatment in the participants undergoing TDM when compared to participants not undergoing TDM.

STUDY SITE/S

TB focal point, Helen Joseph Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
Chief Executive Officer
Tel: (011) 489-0306/1087
Fax: (011)726-5425
Email:Raymond.Billa@gauteng.gov.za

BRIEF OUTLINE OF METHODOLOGY

The planned protocol includes a study group (n=40) of patients with MDR-TB being treated with kanamycin undergoing therapeutic drug monitoring (TDM) and hearing monitoring compared to a study group (n=40) being treated with kanamycin and undergoing hearing monitoring. Baseline and repeated audiological and pharmacological measures will be conducted every two weeks for 3 months per participant and the otoprotective effects of the TDM will be monitored. Creatinine clearance will be monitored at these intervals as well. Participants' daily kanamycin injections will take place at the TB focal point to ensure the correct dosage adjustments can be implemented.

EXPECTED START DATE 5 February 2015		**EXPECTED DURATION** 31 December 2015	
ETHICS CLEARANCE	YES X	NO	PENDING
CONFLICTS OF INTEREST	YES	NO X	DETAILS:
COSTS TO HOSPITAL AND/OR OTHERS	YES	NO X	
SOURCE OF FUNDING	Medical Research Council		
SIGNATURE OF RESEARCHER & DATE	02 Feb 2015		
PERMISSION GRANTED	YES	NO	
SIGNATURE (CLINICAL MANAGER /CEO)	**NAME IN PRINT & DESIGNATION** DR V. L. MLONGWANA		**OFFICIAL STAMP & DATE** SUPERINTENDENT

South Rand Hospita
Enquiries: Dr. M. Maleka
Chief Executive Officer
Tel: (011) 681-2002/2003
Email: mokgadimaleka@gmail.com

PERMISSION TO CONDUCT RESEARCH AT SOUTH RAND HOSPITAL

PRINCIPAL RESEARCHER

FULL NAME	Dr Mohammed Siddique Rassool
DESIGNATION	Senior Medical Officer - Clinical HIV Research Unit
CONTACT NUMBER	Tel: +27 11 276-8800 / Direct: +27 11 276-8813 / Mobile: +27 83 415 8967
E-MAIL ADDRESS	mrassool@witshealth.co.za

DEPARTMENT Clinical HIV Research Unit, Wits Health Consortium, Department of Medicine, University of Witwatersrand, Helen Joseph Hospital, Themba Lethu Clinic

HEAD/S OF DEPARTMENT/S: Prof. Ian Sanne

TITLE OF RESEARCH: A feasibility study investigating the pharmacokinetics of kanamycin and capreomycin in patients with Drug Resistant-Tuberculosis and the relationship between these pharmacokinetics and hearing levels'

AIM OF RESEARCH:
The primary aim is to investigate the relationship between pharmacokinetic measures and hearing levels in patients with DR-TB treated with kanamycin or capreomycin using PTA and DPOAE testing. The relationship between these pharmacokinetic aspects and creatinine results will also be analyzed, as well as overall treatment outcomes after the first three months of treatment.

STUDY SITE/S: South Rand Hospital and Helen Joseph Hospital

BRIEF OUTLINE OF METHODOLOGY:

The study is a multisite study at South Rand Hospital and Helen Joseph Hospital. The planned protocol includes a study group of 80 participants (ages 18 to 55 years) being treated for DR-TB with kanamycin or capreomycin undergoing pharmacokinetic and hearing tests bi monthly for the first three months of treatment. The pharmacokinetic measures and hearing tests will be done at baseline when the participant begins treatment, and subsequently at two weekly intervals. Creatinine function will also be measured. Standard of care procedures will not be interrupted.

EXPECTED START DATE 22 June 2015 | **EXPECTED DURATION** 9 months

ETHICS CLEARANCE	(YES)	NO	PENDING
CONFLICTS OF INTEREST	YES	(NO)	DETAILS:
COSTS TO HOSPITAL AND/OR OTHERS	YES	(NO)	

SOURCE OF FUNDING:
South African Medical Research Council, Wits Health Consortium (CHRU), Sefako Makgatho Health Sciences University

SIGNATURE OF RESEARCHER & DATE 12/06/2015

PERMISSION GRANTED	(YES)	NO	SUID RANDSE HOSPITAL PRIVAAT X1 ROSETTENVILLE 2015 -06- 12
	DR. M. MAKEKA (A/CEO)		ROSETTENVILLE SOUTH RAND HOSPITAL
SIGNATURE (CLINICAL MANAGER /CEO)	**NAME IN PRINT & DESIGNATION**		**OFFICIAL STAMP & DATE**

Appendix C

Screening Consent Form: English

Screening Consent Form: Zulu

Screening Consent Form: SeSotho

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa

Postnet Suite

Screening Consent Form (1.5)

Good day, my name is Cara Hollander and I am an audiologist from the University of the Witwatersrand. I would like to ***invite*** you to think about joining a research study, called "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels"

Before we discuss the study in full (the purpose of the study, benefits, risks and so on), I need to establish whether you fit the specific requirement for this study.

The requirements are as follows:

1. You will need to provide informed consent if you agree to participate (you would only do this if you are suitable for the study, and want to take part)
2. You will need to provide informed consent for an HIV test (we don't mind if you are HIV positive or negative, but we just need the information when we analyze all the results. We will provide you with counseling before and after the test, and you will have time to discuss this in details and ask questions. If you would like further counseling, we will refer you appropriately)
3. Your first language or language of choice must be English, Zulu or Sotho. This is so that we can be sure that you understand the entire study before you chose to take part.
4. You must be anticipated to receive treatment for drug resistant tuberculosis with kanamycin or capreomycin for a period of at least 3 months. We will need to look in your file for this.
5. You must be between the ages of 18 and 55 years
6. You will need to have a normal middle ear status. This means that you can't have any ear infections in your middle ear. We can assess this by doing a quick test. Firstly, I need to look in your ear with a light to see if your ear has too much wax, and if your eardrum looks healthy. If your ear is not blocked up with wax,

Prof. Ian Sanne (Clinical Director); Dr Sharla Badal-Faesen (Investigator); Dr FM Conradie (Investigator); Dr Cindy Firnhaber (Investigator); Dr PD Ive (Investigator); Dr E Jongh (Investigator) Prof P MacPhail (Investigator); Dr K Mellet (Investigator), Dr T Mwelasi (Investigator) Dr MS Rassool (Investigator)

7. I will place a machine in your ear. It is a soft nub and it will pump some air in your ear. It will not be sore, but will help us know if you have any infections deep inside your ear, and if there is any fluid. If there is fluid, it will affect your hearing, and the results of the hearing test.
8. This will take about 2 minutes. In order for us to get an accurate reading of this, your ears must not be blocked with wax. If they are blocked with wax, I will need to take this wax out so it doesn't affect the other tests. I will put some sweet oil in your ear to make the wax a bit softer. Then I will use a special machine to pull the wax out. This whole process will not take longer than 5 minutes. It may be a little bit painful, but isn't always. It is very possible you won't have wax in your ears, and so we won't need to do this.
9. Your hearing levels need to be in certain limits to take part. If you already have a hearing loss, it can't be 'severe' at 3 or more different pitches in both ears. I need to test if your hearing levels will fit with the requirements of the study. We will do this by putting earphone on you. You will need to listen to 'beeps' and press a button if you hear them. If you don't hear 3 of the beeps in both ears, then you will not be able to take part. If you can hear them, then your hearing is OK for the study.
10. If you are diabetic, you won't be able to take part, and it may affect our results.
11. In you have previous treatment with aminoglycosides within the last 7 months (when given with injections) or with capreomycin, you will not be able to participate in this study. Aminoglycosides will include: amikacin, tobramycin, neomycin or streptomycin.

If you consent to eligibility screening, all the results from these tests as described above, and all the information I obtain from your file will be confidential. Only certain study personnel will have access.

Once we know if you are suitable for the study and fit the criteria, we will discuss the study further. By consenting to the eligibility tests does not mean you have to agree to take part in the study. You only need to decide after everything has been explained with the information booklet.

Do you have any questions?

NO?

YES? If yes, please explain:

INFORMED CONSENT TO PARTICIPATE IN ELIGIBILITY SCREENING TESTS

I hereby confirm that I have been informed by the study nurse/counsellor/sub-investigator ..... *(FULL NAME)* about the nature of the eligibility screening tests for the study titled "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels" (PROTOCOL NUMBER 1.5)

- I have also received, read and understood the above written information about the eligibility requirements and tests.
- I am aware that that if I am eligible, I do not have to agree to take part in the study. I can decide this after the full study has been explained with the informed consent form.
- I understand that all the results for these screening tests will be confidential: only study personnel will have access.
- I consent to participating in the eligibility questions and screening hearing tests
- I consent to allowing the nurse to look in my file for the information that she needs for the study eligibility criteria.

PARTICIPANT

Printed Name Signature / Mark or Thumbprint Date and Time

STUDY SUB-INVESTIGATOR/ COORDINATOR

I, ..., herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Printed Name Signature Date and Time

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT (SUB-INVESTIGATOR)

Printed Name Signature Date and Time

WITNESS (If applicable)

Printed Name Signature Date and Time

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa

Postnet Suite

Ifomu Lemvume Yokuhlunga (1.5)

Sawubona, igama lami ngingu-Cara Hollander, ngingumnakekeli wempilo ephathelene nendlebe (audiologist) e-University of the Witwatersrand.Ngingathanda ***ukukumema*** ukuba ucabange ngokujoyina ucwaningo lokuhlola olubizwa ngokuthi "Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin ihamba kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa".

Ngaphambi kokuba sixoxe ngalolu cwaningo ngokuphelele (inqubo yocwaningo, izinzuzo, izingozi nokunye), kudingeka ngithole ukuthi unazo yini izimfuneko ezithile ezidingaw yilolu cwaningo. Izimfuneko yilezi ezilandelayo:

1. Kuyodingeka unikeze imvume oyinikeza unolwazi uma uvuma ukubamba iqhaza (uyokwenza kanjalo kuphela uma ufaneleka ukuba kulolu cwaningo, futhi ufuna ukubamba iqhaza).
2. Kuyodingeka unikeze imvume esekelwe olwazini yokuhlolelwa i-HIV (asinandaba ukuthi unayo yini i-HIV noma cha, kodwa sidinga nje lolu lwazi lapho sihlaziya yonke imiphumela.Siyokweluleka ngokwengqondo ngaphambi nangemuva kokuhlola, futhi uyoba nesikhathi sokuxoxa kabanzi ngalokhu futhi ubuze imibuzo.Uma ungathanda ukuba uphinde welulekwe ngokwengqondo, siyokuthumela endaweni efanele).
3. Ulimi lwakho lokuqala noma ulimi olukhethayo kumelwe kube isiNgisi, isiZulu noma isiSuthu.Lokhu kwenzelwa ukuba siqiniseke ukuthi uyaluqonda lonke ucwaningo ngaphambi kokuba ukhethe ukubamba iqhaza.
4. Kumelwe ulindele ukuthola ukwelashwa kwesifo sofuba esingezweli emithini nge-kanamycin/nge-capreomycinisikhathi esingengaphansi kwezinyanga ezingu-3.Kuyodingeka sibheke ifayela lakho mayelana nalokhu.
5. Kumelwe ube phakathi kweminyaka engu-18 nengu-55 ubudala.
6. Kuyodingeka ube nesimo sendlebe ephakathi nendawo esivamile.Lokhu kusho ukuthi akufanele kube ukuthi utheleleke ngegciwane maphakathi nendlebe.Singakuhlola lokhu ngokwenza ukuhlola okusheshayo.Okokuqala, kudingeke ngibheke indlebe yakho ngesibani ukuze ngibone ukuthi ayinaso yini isigonogono (wax) esiningi, nokuthi i-*eardrum* yakho ibukeka iphile kahle yini.Uma indlebe yakho ingagcwele isigonogono, ngizofaka umshini endlebeni yakho.Uyigenqezana elincane elithambile futhi uzofaka umoya endlebeni yakho.Ngeke kube buhlungu, kodwa kuyosisiza sazi ukuthi akhona yini amagciwane otheleleke ngawo ekujuleni kwendlebe yakho, nokuthi lukhona yini uketshezi oluphakathi.Uma kunoketshezi, lokho kuzoba nomthelela endleleni ozwa ngayo, kanye

nemiphumela yokuhlola kokuzwa.Lokhu kuyothatha imizuzu engaba ngu-2.Ukuze sithole imiphumela eshaya emhloleni yalokhu, kumelwe kube ukuthi indlebe yakho ayivaliwe isigonogono.Uma ivalwe isigonogono, kuzodingeka ngisikhiphe ukuze singaphazamisi okunye ukuhlola.Ngizofaka amafutha anoshukela kancane endlebeni yakho ukuze ngithambise isigonogono.Ngiyobe sengisebenzisa umshini okhethekile ukuze ngidonse isigonogono ngisikhiphe.Yonke le nqubo iyothatha isikhathi esingengaphezu kwemizuzu engu-5.Kungase kube buhlungu kancane, kodwa akubi buhlungu njalo.Kungenzeka kakhulu ukuthi ungabi naso isigonogono ezindlebeni zakho, futhi uma kunjalo ngeke kudingeke senze lokhu.

7. Izinga lakho lokuzwa kudingeka libe semazingeni athile ukuze ubambe iqhaza.Uma kakade ungezwa ezindlebeni, kumelwe kube ukuthi lokho akukho ‘kubi’ ekuphakameni komsindo okungu-3 noma ngaphezulu okuhlukene ezindlebeni zombili.Kudingeka ngihlole ukuthi amazinga akho okuzwa azohambisana yini nezimfuneko zocwaningo.Sizokwenza lokhu ngokukufaka ama-*earphone*.Kuzodingeka ulalele ‘ama-*beep’* bese ucindezela inkinobho uma uwezwa.Uma ungawezwa angu-3 ala ma-beep kuzo zombili izindlebe, ngeke ukwazi ukubamba iqhaza.Uma uwezwa, kusho ukuthi uzwa ngendlela EFANELE lolu cwaningo.
8. Uma unesifo sikashuke, ngeke ukwazi ukubamba iqhaza, futhi lokho kungase kuphazamise imiphumela yethu.
9. Uma wake welashelwa i-aminoglycosides ezinyangeni ezingu-7 ezedlule (lapho inikezwa ngemijovo) noma nge-capreomycin.Le mithi iyohlanganisa i-amikacin, i-tobramycin, i-neomycin noma i-streptomycin.

Uma uvuma ukuhlungelwa ukufaneleka, yonke imiphumela evela kuloku kuhlola njengoba kuchazwe ngenhla, kanye nalo lonke ulwazi engiluthola kwifayela lakho, kuyoba yimfihlo.Ngabasebenzi bocwaningo abathile kuphela abayokwazi ukufinyelela kulo.

Uma sesazi ukuthi uyafaneleka kulolu cwaningo futhi uyahlangabezana nezimfuneko, siyoxoxa kabanzi ngocwaningo.Ukuvuma ukuhlolelwa ukufaneleka akusho ukuthi kudingeka uvume ukubamba iqhaza ocwaningweni.Kudingeka unqume kuphela ngemva kokuba usuchazelwe yonke into ngencwajana yolwazi.

Ikhona yini imibuzo onayo?

CHA
YEBO

Uma uthi Yebo, sicela uchaze:

IMVUME ESEKELWE OLWAZINI YOKUBAMBA IQHAZA EKUHLOLWENI KOKUFANELEKELA UKUHLUNGA

Lapha ngiqinisekisa ukuthi unesi wocwaningo,

.....(*IGAMA NGOKUGCWELE),* ungazisile ngesimo sokuhlolwa kokufanelekela ukuhlunga kocwaningo olunesihloko esithi "Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin ihamba kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa"" (INOMBOLO YEPHROTHOKHOLI 1.5).

- Ngiphinde ngathola, ngafunda futhi ngaluqonda lolu lwazi olubhalwe ngenhla mayelana nezimfuneko zokufaneleka nokuhlola.
- Ngiyazi ukuthi uma ngifaneleka, angiphoqekile ukuba ngibambe iqhaza ocwaningweni.Nginganquma lokho ngemva kokuba sengichazelwe ngokuphelele ucwaningo ngefomu lemvume esekelwe olwazini.
- Ngiyaqonda ukuthi yonke imiphumela yoloku kuhlola kokuhlungwa iyoba yimfihlo:ngabasebenzi bocwaningo kuphela abayokwazi ukufinyelela kuyo.
- Ngiyavuma ukubamba iqhaza emibuzweni yokuhlola ukufaneleka nokuhlolwa kokuzwa kokuhlunga.
- Ngiyavuma ukuba unesi abheke ifayela lami ukuze athole ulwazi aludingayo mayelana nezimfuneko zokufanelekela ucwaningo.

UMBAMBIQHAZA

Igama Eliphrinti	Isiginesha/Uphawu noma Ukugingqa Isithupha	Usuku Nesikhathi

UMCWANINGI ONGAPHANSI WOCWANINGO

Mina, ..., lapha ngiqinisekisa ukuthi lo mbambiqhaza ongenhla utshelwe ngokuphelele ngesimo, ukuqhutshwa nezingozi zocwaningo olungenhla.

Igama Eliphrintiwe	Isiginesha	Usuku Nesikhathi

UMHUMUSHI / OMUNYE UMUNTU OCHAZA IMVUME ESEKELWE OLWAZINI (UMCWANINGI ONGAPHANSI)

Igama Eliphrintiwe	Isiginesha	Usuku Nesikhathi

UFAKAZI (Uma ekhona)

Igama Eliphrintiwe	***Isiginesha***	***Usuku Nesikhathi***

Foromo ya Tumello ya Tlhahlobo (1.5)

Dumela, lebitso la ka ke Cara Hollander mme ke audiologist (setsebi sa medumo e utlwahalang) ho tswa ho University of the Witwatersrand. Ke rata ho o ***mema*** ho nahana ka ho kenela patlisiso ya phuputso e bitswang "Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng tsa ditekanyo tsa ho utlwa ditsebeng".

Pele re qoqa ka phuputso ka botlalo (sepheo sa phuputso, melemo, dikotsi jwalo jwalo), ke hloka ho thea hore o kgotsofatsa dintho tse hlokwang tse kgethehileng bakeng sa phuputso ena.

Dintho tse hlokwang ke tse latelang:

1. O tla hloka ho nehela ka tumello e utlwisiswang ha o dumela ho nka karolo (o ka etsa hona feela ha o tshwanelehile bakeng sa phuputso, mme o batla ho nka karolo).
2. O tla hloka ho nehela ka tumello e utlwisiswang bakeng sa tekolo ya HIV (ha re tsotelle hore o na le HIV kapa ha o na yona, empa re hloka feela tlhahisoleseding ha re hlopholla diphetho. Re tla nehela ka boeletsi ho wena pele le ka mora tekolo, hape re tla ba le nako ya ho qoqa ka botebo le ho botsa dipotso. Ha o batla boeletsi bo eketsehileng, re tla o romela ka ho tshwanelehileng).
3. Puo ya hao ya pele kapa puo ya kgetho e tlameha ho ba Senyesemane, Sezulu kapa Sesotho. Hona ke hobane re batla ho etsa bonnete hore o utlwisisa phuputso yohle pele o kgetha ho nka karolo.
4. O tlameha ho lebella ho fumana kalafo bakeng sa lefuba le hanyetsang moriana ka kanamycin kapa capreomycin bakeng sa nako ya dikgwedi tse 3 bonyane. Re hloka ho sheba faeleng ya hao bakeng sa hona.
5. O tlameha ho ba pakeng tsa dilemo tse 18 le tse 55.
6. O tla hloka ho ba le boemo ba bohare ba tsebe bo tlwaelehileng. Hona ho bolela o ka se be le tshwaetso efe kapa efe ya tsebe ho bohare ba hao ba tsebe. Re ka lekanya ka ho etsa tekolo e phakisang. Pele, ke hloka ho sheba ka hara tsebe ya hao ka lebone ho bona ha tsebe ya hao e na le boka bo bongata haholo, le ha moropa wa tsebe (eardrum) ya hao o bonahala o phetse. Ha tsebe ya hao e sa thibana ke boka, ke tla beha motjhini tsebeng ya hao. Ke kotola e bonolo mme e tla pompa moya o itseng tsebeng ya hao. E ka se be bohloko, empa e tla re thusa ho tseba ha o na le tshwaetso ka hare botebong ba tsebe ya hao, le hore ho na le mokedikedi ofe kapa ofe. Ha ho na le mokedikedi, ho tla ama ho utlwa ha hao, le diphetho tsa tekolo ya ho utlwa. Hona ho tla nka mabapi le metsotso e 2. Hore re kgone ho fumana

tekanyetso e nepahetseng ya hona, ditsebe tsa hao di tlameha di se ke tsa thibana ke boka. Ha di thibane ke boka, ke tla hloka ho ntsha boka bona hore bo se ke ba ama diteko tse ding. Ke tla tshela sutu-oli e itseng tsebeng ya hao ho etsa boka bo be bonojwana. Ka mora moo ke tla sebedisa motjhini o kgethehileng ho ntsha boka. Tshebetso ena yohle e ka se nke ho feta metsotso e 5. E ka ba bohloko hanyane, empa ha ho atise ho ba jwalo. Ho na le kgonahalo e kgolo ya hore o ka se be le boka ditsebeng tsa hao, mme re ke ke ra hloka ho etsa hona.

7. Mephahamo ya hao ya ho utlwa e hloka ho ba meeding e itseng hore o nke karolo. Ha o se o na le tahlehelo ya ho utlwa, e ke ke ya ba 'bohale' ka dihalo tse 3 kapa ho feta tse fapaneng ditsebeng ka bobedi. Ke hloka ho lekola ha mephahamo ya hao ya ho utlwa e tla lokela ditlhoko tsa phuputso. Re tla etsa hona ka ho beha semamela-tsebeng (earphone) ho wena. O tla hloka ho mamela 'medumo e mekgutshwane e phetaphetang' mme o tobetse konopo ha o e utlwa. Ha o sa utlwe medumo e mekgutshwane e phetaphetang e 3 ditsebeng ka bobedi, kahoo o ke ke wa kgona ho nka karolo. Ha o ka e utlwa, kahoo ho utlwa ha hao ho LOKILE bakeng sa phuputso.
8. Ha o na le lefu la tswekere (diabetic), o ke ke wa kgona ho nka karolo, ho ka ama diphetho tsa hao.
9. Ha o na e kalafo ya ka pele ya aminoglycosides nakong ya dikgwedi tse 7 tse fetileng (ha e nehwa le diente) kapa le capreomycin. Meriana ena e tla kenyeletsa amikacin, tobramycin, neomycin kapa streptomycin.

Haeba o dumela ho etsa tlhahlobo ya ho tshwaneleha, diphetho tsohle tse tswang ditekong tsena jwalo ka ha di hlalositswe ka hodimo, le tlhahisoleseding yohle eo ke e fumaneng faeleng ya hao e tla ba sephiri. Ke basebetsi ba phuputso ba itseng feela ba tla ba le phihlello.

Hang ha re tseba hore o tshwanelehile bakeng sa phuputso mme o kgotsofatsa ditlhokeho, re tla qoqa ka phuputso ho tswela pele. Ka ho dumela ho diteko tsa ho tshwaneleha ha ho bolele hore o dumela ho nka karolo phuputsong. O hloka feela ho nka qeto ka mora hore dintho tsohle di hlalositswe le bukana ya tlhahisoleseding.

Na o na le dipotso dife kapa dife?

TJHE
E

Ha o re E, ka kopo hlalosa:

TUMELLO E UTLWISISWANG YA HO NKA KAROLO DITEKONG TSA TLHAHLOBO YA HO TSHWANELEHA

Ka hona ke tiisa hore ke tsebisitswe ke mooki wa phuputso,..... *(LEBITSO KA BOTLALO)*, mabapi le mokgwa wa ditekolo tsa tlhahlobo ya ho tshwaneleha bakeng sa phuputso ya sehloho se reng "Phuputso ya patlisiso ya kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng ditekanyo tsa ho utlwa ditsebenga" (NOMORO YA PROTHOKHOLE 1.5).

- Hape ke fumane, ka bala mme ka utlwisisa tlhahisoleseding e ka hodimo e ngotsweng mabapi le ditlhoko le ditekolo tsa ho tshwaneleha.
- Ke a lemoha hore ha ke tshwaneleha, ha ho hlokehe hore ke dumele ho nka karolo phuputsong. Nka etsa qeto ka mora hore phuputso e feletseng e hlalositswe le foromo ya tumello e utlwisiswang.
- Ke a utlwisisa hore diphetho tsohle tsa ditekolo tsena tsa tlhahlobo di tla ba sephiri: Ke basebetsi ba phuputso feela ba tla ba le phihlello.
- Ke dumela ho nka karolo ho dipotso tsa ho tshwaneleha le diteko tsa ho utlwa tsa tlhahlobo
- Ke dumela ho dumella mooki ho sheba faele ya ka bakeng sa tlhahisoleseding eo a e hlokang bakeng sa ditlhoko tsa ho tshwaneleha tsa phuputso.

MONKAKAROLO

Lebitso le hatisitsweng	Tshaeno / Letshwao kapa Kgatiso ya Monwana o Motona	Mohla le Nako

MOTHUSI WA MOFUPUTSI WA PHUPUTSO

Nna, ..., ka hona ke tiisa hore monkakarolo ya ka hodimo o tsebisitswe ka botlalo mabapi le mokgwa, tsamaiso le dikotsi tsa phuputso e ka hodimo.

Lebitso le hatisitsweng	Tshaeno	Mohla le Nako

MOFETOLEDI / MOTHO E MONG YA HLALOSANG TUMELLO E UTLWISISWANG (MOTHUSI WA MOFUPUTSI)

Lebitso le hatisitsweng	Tshaeno	Mohla le Nako

PAKI (Ha e hlokeha)

Lebitso le hatisitsweng	Tshaeno	Mohla le Nako

Appendix D

Screening Case Report Form

Kanamycin Study **Clinical HIV Research Unit** **Visit: Screening**

Visit Date: _____ (DD.MMM.YYYY) Initials: _____ **Study Number:**

Visit: Screening (Day 1)

Procedures	Yes	No
Screening Consent 1 done		
Standard of Care bloods Done:		
Creatinine (Cr,GRF) (send results to SMU)		
Potassium (K)		
TSH		
Liver Enzymes (GGT,Alt, Bili)		
FBC		
CD_4		
Audiology		
Screening Audiology (otoscopy, cerumen management if needed, immitance audiometry, screening pure tones)		
Inclusion/Exclusion Criteria Form		

Visit: Screening (Day 1)

Time: *(HH:MM)* **I___I___I:I___I___I**

Weight	**Height**
I__I__I__I. I__I kg	**I__I__I__I. I__I cm**

Subject Details	
Subject Name *(First name middle name surname)* _____ **Date of Birth***(DD.MMM.YYYY)* I___I___I.I___I___I___I.I___I___I___I___I	Subject initials I___I___I___I
Race✓ Gender M I__I F I__I I__I Black I__I White I__I Mixed I__I Asian I__I Other _____ **Ethnicity** specify _____	
Subject's History	
➔ Social History	
Marital status ✓ I__I Married I__I Single I__I Living in relationship I__I Divorced I__I Other _____	

Highest level of Education ✓			Occupation ✓
I__I	less than standard 8	I__I	I__I employed as _____
	standard 8		
I__I	standard 9	I__I	I__I unemployed
	standard 10		
I__I	tertiary education		

➔ Medical History

Smoking history

Does the subject have a history of smoking? ✓

I__I Yes ⇒ **Pack/week** _____

I__I No

Does the subject currently smoke? ✓

I__I Yes ⇒ **Amount/day** _____

I__I No

Alcohol history Does the subject drink alcohol? ✓ I__I Yes ⇒ I__I No		**Type**	**Amount (ml)**	**Units**
	Drink/day			
	Drink/week			
	Drink/Occasionally			
Does the subject abuse substances? ✓ I__I Yes ⇒ **Type**_____ I__I No				

Surgical history?✓ I__I No I__I Yes ⇘		
Type	**Date**	**DateUnknown**
		I__I
		I__I
		I__I

Have you ever been hospitalized?	No I__I Yes I__I		
Did you previously have TB?	No I__I Yes I__I		
How many times?			
Where were you treated?			
For how long?			
What medication did you take?			
Time and date of last dose of kanamycin			
Have you had or do you have:		**If so, when Start Date**	**Stop Date**
Measles?	No I__I Yes I__I		
Mumps?	No I__I Yes I__I		
Chronic ear infections?	No I__I Yes I__I		
Encephalitis?	No I__I Yes I__I		
Meningitis?	No I__I Yes I__I		
Cancer?	No I__I Yes I__I		

Diabetes?	No I__I Yes I__I		
Have you ever been in an accident which resulted in a head injury or trauma to the head?			
Are you pregnant or plan to become pregnant during this study?			
Would you consent to an HIV test			
Are you fluent in Zulu, Sotho or English			

Ototoxic Medication Checklist

Have you ever been treated with any of the following medications (ask for permission to look in participant file and get the information)? Please tick the medications you have been treated with, and cross the medications you have not been treated with.

Salicylates		**Antibiotics**	
Aspirin (>6-8 tablets per day)		Aminoglycosides	
Non-Steroidal Anti-inflammatory Drugs		Gentamicin (Garamicin□, Septopal□)	
Ibuprofen (Brufen□)		Amikacin	
Indomethacin (Arthrexin□, Betacin□)		Tobramycin (Nebcin□)	
Naproxen (*>6-8 tab's per day)* (Aleve□)		Netilmicin (*when given IV)* (Netromycin□)	
Diclofenac (Voltaren□, Cataflam D□, Veltex□)		Kanamycin	
Mephenamic acid (Ponstan□, Ponac□)		Streptomycin	
Quinine		Neomycin	
Loop Diuretics		**Macrolides**	
Furosemide (Lasix□, Puresis□, Beurises□, Uretic□)		Clarithromycin (Klacid□, Clacee□, Klarithan□)	
Bumetanide (Burinex□) *(When given IV)*		Ketolides (Telithromycin) (Ketek□)	
Torasemide (Unat□,Torahexal□)		Erythromycin *(2-4g per 24h, IV only)* (Erymycin□,Ilosone□,Betamycin□)	
Piretanide (Arelix□)		Azithromycin (Zithromax□, Azimax□, Binozyt□)	
Chemotherapeutic agents		Glycopeptide	

Platinum compounds					
Cisplatin (Abiplatin□, Platosin□)					
Carboplatin (Carbosin□, Paraplatin RTU□)					
Oxaliplatin (Eloxatin□, Oxaliwin□)					
Iron – Chelating					
Deferoxamine (Desferal□)					
Vinca Alkaloids					
Vincristine					
Vinblastine					
Vinorelbine (Navelbine□)					
Nitrogen Mustard analogues					
Cyclophosphamide (Endoxan□)					
Chlorambucil (Leukeran□)					
Melphalan (Alkeran□)					
Ifosfamide (Holoxan□, Ifolem□)					
Vancomycin *(when given IV)* (Vancocin CP□)					
Peptide					
Capreomycin (Capastat□)					
Add ARV regimens					
NNRTIs					
Delavirdine		Nevirapine			
Efavirenz		Rilpirivine			
Etravirine					
NRTIs					
ABC		D4T			
d		TDF			
FTC		ZVD			
3TC					
Protease Inhibitors					
ATV		NFV			
DRV		RTV			
FPV		SQV			
IDV		TPV			
LPV					
Entry & Integrase Inhibitors					
EVG & Cobi		RAL			
MVC					

Audiological History

Do you struggle to hear? If so, please elaborate? (when, how often, in what situations, when did it start, does it fluctuate, what sounds, examples etc)	
Has anyone else told you that you struggle to hear? If so, please elaborate.	
Do you have a family history of hearing loss? If so, please elaborate.	
Have you ever had your hearing tested? If so, please elaborate.	
Do you have, or have you ever had a hearing aid?	
Have you been exposed to very loud noises for a long time? (work in factories, army/police force, band or loud music daily)	
Do you ever have tinnitus? (Ringing or sounds in your ears). If so, what kind of sounds, in both ears, how often, for how long?)	
Do you have ear pain?	
Do you ever have smelly discharge coming out of your ears?	
Are you able to know where the sound is coming from? (Localize)	

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tympanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Pure Tone Audiometry (AC) (Screening Audiometry): Right Ear (dB)/Left Ear (dB)

Consistent	Co-operative	Other

Signature/Initials		Date	

Inclusion/Exclusion Criteria		
Inclusion Criteria	**YES**	**NO**
Consent provided by participant		
Consented to HIV test (if not already done and results in their hospital file)		
First language is/language of choice is English, Zulu or Sotho.		
Receiving treatment for DR-TB with kanamycin/capreomycin for a period of at least 3 months		
Participant between the ages of 18 and 55 years		
Normal middle ear status as determined by screening otoscopy and tympanometry (not a type B or C)		
Exclusion Criteria		
Diabetes Mellitus		
Previous treatment of aminoglycosides within the last 7 months when given intravenously. These drugs will include: amikacin, tobramycin, neomycin or streptomycin.		
Previous treatment with kanamycin/capreomycin within the last 7 months. However, should they have taken up to 3 dosages of kanamycin prior to enrolment (within a week prior to enrolment), then the participant will still be included.		
Middle ear pathology		
Severe or profound hearing loss in at 3 or more frequencies above 2000Hz in both ears.		
Significant history of substance abuse that may affect adherence to protocol		

	YES	NO
Does the patient qualify to be enrolled on the study?(If no, state reason)		

Appendix E

Information Leaflets and Informed Consent Form for **Helen Joseph Hospital**: English

Information Leaflets and Informed Consent Form for **Helen Joseph Hospital**: Zulu

Information Leaflets and Informed Consent Form for **Helen Joseph Hospital**: SeSotho

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa
Postnet Suite

INFORMED CONSENT VERSION NUMBER: 1.5

(Helen Joseph Hospital)

STUDY TITLE: A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels

INSTITUTION: University of the Witwatersrand in collaboration with Sefako Makgatho Health Sciences University

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S): 082 815 8878 (Cara Hollander) and/or 011 276 8968 (Dr. Rebecca Berhanu - Doctor) and /or +27 11 276-8813 (Dr. Mohammed Rassool – Principal Investigator – Doctor at Helen Joseph – Wits Health Consortium)

STUDY COORDINATOR: Matshediso Mkhwanazi: speed dial: 50017/ 076 711 2874/ Matshidiso.Mkhwanazi@righttocare.org

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor/nurse or the study staff to explain any words or information that you do not clearly understand. You may keep* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

INTRODUCTION

Good day, my name is Cara Hollander and I am an audiologist from the University of the Witwatersrand. I would like to ***invite*** you to think about joining a research study, called "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels". We have just done some tests to confirm that you fit the criteria to take part in this study.

Prof. Ian Sanne (Clinical Director); Dr Sharla Badal-Faesen (Investigator); Dr FM Conradie (Investigator); Dr Cindy Firnhaber (Investigator); Dr PD Ive (Investigator); Dr E Jongh (Investigator) Prof P MacPhail (Investigator); Dr K Mellet (Investigator), Dr T Mwelasi (Investigator) Dr MS Rassool (Investigator)

1. Before agreeing to take part in this study, it is important that you read and understand the following explanations about the reason for the study, the study procedures, benefits, risks, uncomfortable aspects, and precautions as well your right to pull out from the study at any time.

2. This information booklet is to help you to decide if you would like to take part. You need to understand everything about the study before you agree to take part in this study.

3. If you have any questions, please ask me.

4. You should not agree to take part unless you are happy about all the parts involved.

5. You may not take part in another research study while you are taking part in this study (unless it is approved by me beforehand).

6. Please be open with me about your health history, since you may otherwise harm yourself by taking part in this study.

7. If you decide to take part in this study, you will be asked to sign this form to confirm that you understand the study. You will be given a copy to keep.

8. If you have a personal doctor outside of this hospital, please discuss with or tell him/her of your possible participation in this study. If you would like, I can also tell your personal doctor about this.

PURPOSE OF THE STUDY

You are in this hospital/clinic because you have Drug Resistant Tuberculosis (DR-TB). I would like you to think about taking part in the research to measure your hearing levels throughout your DR-TB treatment. You will be receiving medicine (injections) to treat your drug resistant tuberculosis called kanamycin together with a few other medications, so that you can get better from your TB, which is very important. The medicine you will be receiving is very strong, and has a few risks and one of them is hearing loss. However, you need to take this medicine so that you can get healthy again. Many people who take the medication will lose some of their hearing; but, although this happens often, it does not happen always. It can be very hard to talk to family and friends with a hearing loss and working can also be difficult. Therefore, during this research, we want to measure your hearing 7 times in the first three months, so that we can understand exactly what happens to your hearing. Then, we would also like to do blood tests 8 times in the first 3 months, so that we can look how your medicine for your DR-TB is working in your body. We will not changing or adjusting your DR-TB medicine based on the blood tests, but it will allow us to understand how the medicine works differently in different people, so that we can hopefully try and prevent hearing loss in the future. Your assistance will help us treat

other patients in the future with this illness and it will also allow us to monitor your hearing throughout, and look at a relationship between how the drug is used in your body with your hearing.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS

The study will take place at this hospital as well as at South Rand Hospital. About 80 people will take part in this study. The participants will be between the ages of 18 and 55 years. You will need to take your kanamycin for more months than you will be part of this study. We will be doing tests for three months for this study, which will be explained below. These tests are blood tests and hearing tests. In the first 3 months, you will be asked to visit me 9 times for tests during the study. We will need you to come back to the clinic for all these tests. Today will be counted as day 1. Sometimes they will be on the same day as your general clinic visits. You will ALSO need to come to either this clinic or the clinic closest to your home every day to get your kanamycin injection from a nurse so she can record the time and dosage you are receiving. You will therefore need to come to this clinic at Helen Joseph Hospital once every second week for the hearing and blood tests, and then the local clinic daily (unless you choose to come to Helen Joseph daily). We will give you R150 for your travelling expenses every time you need to come to the hospital for the hearing and blood tests. This will be for 9 times, every second week. If you are an inpatient in the hospital, you will not be paid for your transport, until you get discharged, as you will not need money for your transport. Then, we will give you enough money for your transport to go to the local clinic every day (from Monday to Friday) to get your kanamycin injections. We will give you R50 for your transport to the clinic every day. When you come to the Helen Joseph clinic for your 'official' study visits, when you have the hearing and blood tests we will give you R150. You will not get extra transport money that you get daily for coming for your injections on the days that you get R150.

PROCEDURES

If you agree to take part in this study, you will be asked questions and then will need to undergo a few tests – which will be hearing tests and blood tests. These tests will need to be done in addition to your other tests/procedures that are not study related.

If you agree to take part in this study and consent, I will need to ask you some questions today and examine you. Then, you will need to come back tomorrow as well for your blood tests and the first hearing tests.

You will need to come here, or to your local clinic every day (from Monday to Friday – not on the weekends) to get your kanamycin injection. Then, every second week, you will need to have blood tests and hearing tests. These days will take longer than your daily visits.

Purpose of hearing tests

Our ears are wonderful organs because they can hear so many difference pitches. We can hear low pitches which are for example a lawn mower, or a bus, or even a tap dripping. These are different sounds, and have different loudness levels, but they all have low pitches. Then we can also hear high pitches, for example birds tweeting or alarm clocks ringing.

Speech sounds, words and sentences are all different pitches. Like for example, the /m/, /d/ and /b/ are lower pitches where-as the /f/, /s/ and /th/ are higher pitches. In order for us to understand each other, we need to be able to hear many different frequencies or pitches, as speech sounds have many different pitches.

As soon as we start to only hear low pitches, and not the high pitches, then we struggle to understand speech. So, for example, when someone is saying ‘head’, you may mishear, and hear ‘bed’. If someone says ‘fate’, you may hear ‘ate’. Therefore a hearing loss at even a few frequencies will make it difficult to understand friends, family and doctors.

Many different things can cause hearing loss. Sometime people can be born with a hearing loss, or it could be from loud noise, trauma and some medicines. DR-TB is a serious illness, and you need very strong medicine to recover and live. However, sometimes, these medicines can cause a hearing loss, which could make it difficult for you to hear and communicate.

As the strong medicine (kanamycin) is needed to live, you have to take it. BUT, this research is to try to understand the exact kind of hearing loss that is caused by the medicine which will better allow for treatment or prevention in the future. We need to measure how you hear all the different sounds and pitches when you come into hospital, and then every few weeks, to see if its staying the same, or getting worse.

Hearing test procedures

A hearing test is not painful, and there are a few parts, as follows:

- Otoscopy – Firstly, I will need to look in your ears with a light to see if there is any wax, or other things in your ears, as this can affect your results. This will take about 20 seconds.

- Cerumen management – if your ears are clogged with wax, I will take the wax out so it doesn't affect the other tests. I will put some oil in your ear to make the wax soft. Then I will use a machine to pull out the wax (suction). The suction will only take a few seconds. It may be slightly painful, but it is not always painful.
- Tympanometry – Then, I will place a machine in your ear. It is a soft nub and it will pump some air in your ear. It will not be sore, but will help us know if you have any infections deep inside your ear, and if there is any fluid. If there is fluid, it will affect your hearing, and the results of the hearing test. This will take about 2 minutes.
- Distortion Product Otoacoustic Emissions – We have tiny hair cells deep in our ears. The different hair cells are important to hear the different pitches. Therefore, and DPOAE machine measures how these hair cells are moving and working. We need to put a soft nub in your ear, and it will make different sounds. You need to keep still and quiet, and the machine will take the measurements of these hair cells. This will take about 5 to 10 minutes.
- Pure Tone Audiometry – we will put headphones on you. They will give off very soft sounds. The sounds will have different pitches. Some will be low, and some will be high. Whenever you hear a sound, you will need to press a button. This will take about 15 to 20 minutes.

Once this is done, we are able to put all the results together and understand exactly what you are hearing. If we do the test when you come into hospital, and then we do it again at certain intervals, we can see if your hearing is changing.

If you agree to this, you will need to do this 7 times in the first 3 months. It would be tomorrow, then every second week for the next 3 months.

After 3 months of the study, you will continue to have your hearing monitored by the audiologists at this hospital or the hospital or clinic in your region. Should you get a hearing loss, they will continue to help you with hearing aids and further management. I will refer you to them after the study.

Blood Sampling

We will need to take blood as well. We will need to take blood so that we can measure how the DR-TB treatment (kanamycin) is being used in your body. We hope this will help us understand why people get a hearing loss. Myself, or another nurse, doctor or phlebotomist will take blood from you so that we can do the necessary tests. We need to take 2mls of blood for each test. You will need to have at least

2 blood tests each time (except for the first 2 visits). Two mls is about 2 drops of blood or half a teaspoon. Therefore, we will need to take 4mls of blood each day we see you to measure the kanamycin (just under a teaspoon of blood). The first time will be a few hours after you get your injection for your DR-TB. Then, the second time will be the following day before you get your injection. And the other times, you will need to get your blood taken before your injection, and a few hours after your injection. Therefore, for each visit (besides for the second visit when you have blood tests), you will need to be at the clinic for at least 4.5 hours. We will need to do this 8 times all together over 3 months (tomorrow will be the first time). So altogether, over the 3 months, we will take a total of 28mls of blood, which is about 5 and a half teaspoons. We will therefore just be taking the blood and doing the hearing tests.

Then, in order to understand how the medicine may be affecting your kidneys, we would like to measure kidney function as well. On 3 out of the 9 visits, we will also need to take another 3 mls of blood, so we can measure your kidney function and make the correct dosage changes. Therefore on the visits that we will need to test this, we need an extra 3mls of blood, with is just over half a teaspoon. Altogether, over the 3 times, we will draw 9 mls or blood, which is just under two teaspoons addition to the other blood tests described above. We will draw this at the same time at the blood test for the kanamycin – so that there will not be an extra needle prick.

Taking blood is part of your normal medical care at this hospital. We will need to take blood separately to the regular hospital procedures. This may present a slight risk of discomfort. We will draw the blood in the same way as it is taken for your general blood tests. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Experienced nurses, doctors or phlebotomists will take the blood in clean conditions to help make sure that is will be safe.

Your blood will be kept safely at Helen Joseph Hospital until it is sent to the laboratory to be tested. It will be sent as soon as possible. It will not be kept for more than a week. Your blood will be sent to a laboratory at Sefako Makgatho Health Sciences University. Then, the blood we take to measure your kidney function will be sent to another laboratory, called CLS. All the personal information about these tests and about your general health will be kept private in a file and then in a cupboard during after the research study. Personal information will not be discussed with any person not involved in the research study. If this is needed, we will ask for your permission before this is done.

The hearing tests and blood tests will be done on day 2 (tomorrow), days 15, 28, 40, 54, 68 and 84. The blood tests will take place tomorrow (day 2), the next day (day 3), and then on the same day as the hearing tests - on days 15, 28, 40, 54, 68 and 84.

At every visit that you come for the hearing and blood tests (not the days in between when you just come for your injections), each visit will take about 5 to 6 hours. This is because we need to wait about 4 to 6 hours between the 2 blood tests. So, it would be best if you came early in the morning, so you can leave by the afternoon.

WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

Taking blood may cause a small discomfort. We will take the blood in the same way as it is taken for your other blood tests. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding in the area that we take the blood from. There is also a slight chance of infection. Only experienced nurses (or phlebotomists or doctors) will take your blood to help protect you and everything will always be clean. A total of 4 mls of blood (i.e. just under a teaspoon) will be taken on each study visit (besides for day 2 and day 3 – only 2mls will be taken). This is a total of 28 mls, which is about 5 and a half teaspoons of blood. Then, an extra 3 mls will be drawn on days 40, 68 an 84 – an extra total of 9mls which just under 2 teaspoons. Therefore, all together, 37 mls will be drawn over the three months – which is equivalent to about 7 and a half teaspoons.

The hearing tests as described above will not cause discomfort; however, taking out the wax may be slightly painful. We do not need to take out wax for every person though, and it is not always sore. Taking out the wax will only last a few seconds though. The rest of the test will take approximately 30 to 40 minutes of your time for each visit. You will always be able to discuss your results with the nurse and ask questions before or after these tests. If you have more questions, you can get in touch with myself, who is an audiologist.

BENEFITS

- The possible benefit from your participation in this study is you will be able to understand your hearing status in more detail, and its relationship with how the kanamycin is being used in your body.
- You may not benefit from this study.
- Your participation in this study will help develop medical knowledge that may help other patients that, like you, have DR-TB and are at risk to develop a hearing loss.

ALTERNATIVE TREATMENT

- At the moment, there is no treatment to reduce or prevent the hearing loss caused by DR-TB medicine. Should you get a hearing loss; you will be referred to the local clinic nearest to you to assist you to receive a hearing aid.
- Monitoring the kanamycin in your blood is not a standard procedure, and there is no other way besides blood tests to do this at the moment.
- The Audiology Department at this hospital will be able to assist you if you are in this catchment area. This is part of general government procedures with hearing loss management.
- If you decide not to take part in this study you will still receive the best current care at this clinic for your DR-TB.

BENEFITS AND RISKS OF STANDARD ALTERNATIVE TREATMENT

- As there is currently no medicine that can help to prevent or lessen hearing loss, there is no other treatment. If your DR-TB medication causes a hearing loss, it is permanent, and cannot be fixed. But it will be possible to get a hearing aid to make all the sounds louder to help you. Hearing aids however cannot always help with hearing loss, as sometime the hearing loss is so bad, that the hearing aids cannot help. We will not be giving you the hearing aids – the hospitals audiology department will be able to assist you with that if you are in this catchment area, or we will refer you to the correct clinic or hospital that is in your catchment area.
- The benefits of the hearing aids can be limited, however may help you if you develop a hearing loss from your DR-TB medication. Hearing aids do not have any risks.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY

- If you have Diabetes Mellitus you may not take part in this study. Diabetes Mellitus can sometimes affect the hearing, and we want to be able to measure your hearing without this possibly interfering.
- If you are any younger than 18 years of age, or older than 55 years of age, you may not take part in the study. In this study, we are only measuring people between the ages of 18 and 55 years.
- If your doctor changes your medication, you may not be able to continue participating in this study.
- If you have been addicted to any drug and have a history of drug or alcohol abuse, you cannot take part in the study if this could impact in your compliance with the test procedures. This will be decided at the discretion of the investigators involved.

RIGHTS AS A PARTICIPANT IN THIS STUDY

Voluntary

Your participation in this study is entirely voluntary and you can choose if you would like to take part or not. You can also stop taking part at any time and you do not need to give a reason. If you chose to not take part, or decide to stop taking part during the study, you will still get the medical care at this hospital, and it will not be affected.

New findings

I will provide you with any new information that I have during the study, which may change your willingness to continue on the study

Withdrawal

Your withdrawal or stopping participation in the study will not affect your other medical care. I have the right to withdraw you from the study if it is what is best for you. If your doctor changes your medicine for the DR-TB and you will not be taking kanamycin, then you will not be able to continue with this study. If you did not give correct and truthful information about your medical history, or did not follow the rules of the study, I may take you off the study at any time.

EMERGENCY CARE AND HOSPITALISATION

If you need emergency care at any time during the study, please call Dr. Mohammed Rassool on 011 276-8813 or 027 83 415 8967 or Dr. Rebecca Berhanu on 011276 8968 or 072 717 9159.

FINANCIAL ARRANGEMENTS

- The funders of this study will provide payment for all study tests.
- Neither you nor your medical aid (if you have one) will need to pay for any study medication or study procedures, and they have been all funded by research organizations.
- When you visit the hospital for the study every second week (for hearing and blood tests) you will be provided with R150 for your transport. You will not be paid to take part, but only for your transport and refreshments. When you go to your local clinic daily, you will be compensated for your transport. You will be provided with R50 to go to your local clinic daily. This will only be for the first 3 months. After these 3 months, no money will be provided for your transport.

ETHICAL APPROVAL

- This clinical study protocol has been given to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been given by that committee.
- The study follows the guidelines of the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations for doctors in doing medical research with human participants. If you would like a copy of these principles, please let me know, and I will get them to you.
- This study is paid for by a research organisation (South African Medical Research Council). I do not have any financial or personal interests with this organization and I am not influenced or biased by them.

INSURANCE

All the medical doctors in this study have insurance. The principal investigator and doctors are insured by MPS to conduct the procedures as long as:

- They obey the procedures of the study protocol.
- Their compliance with the rules of the Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication according to the protocol and amendments and other related documents.
- The indemnification is not intended to be and is not a substitute for any personal malpractice insurance.

Please note that if you have a life insurance policy you should find out if your insurance company needs to be notified about you taking part in the study. From other information, this should not affect any life insurance policy taken out. But it is still important to double check this as sometimes companies are different.

SOURCE OF ADDITIONAL INFORMATION

During the study, you will be cared for by the staff at Helen Joseph Hospital. If at any time you feel that you have further study related questions, please contact me or the study nurse/coordinator on duty at the hospital.

Members of the study who you can contact:

- Cara Hollander – 082 815 8878 (Audiologist)
- Dr. Karin Joubert – 011 717 4561 (Audiologist)
- Professor. Natalie Schellack – 012 521 3286 (Pharmacist)
- Dr. Rebbeca Berhanu – 011 276 8968 (Doctor)
- Dr. Mohammed Rassool –011 276-8813 (Doctor and Principal Investigator)

If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee to help protect the rights of research participants at (011) 717 2301.

For **research information** you can contact the Study Planner– Cara Hollander from the University of the Witwatersrand on 082 815 8878.

CONFIDENTIALITY

- All information that we collect during this study, which includes hospital records, personal and research information will be kept strictly confidential. Only members of the research team, and your doctors and nurses will have access to your information. Any information that will be written in scientific journals or anything that is published will not have your name on.
- We will put different codes on your study information. Therefore, when reviewing your results, there will only be a code. Your name, identity number or any other identifying notes will not be on the documents, to ensure everything is confidential.
- This information will be reviewed by authorised representatives of the University of the Witwatersrand and Sefako Makgatho Health Sciences University as well and members from the funders (Medical Research Council). Auditors of the Wits Health Consortium may look at some of the results when they do their inspection to make sure everything is done with good

standards. However, not everyone will have access to your name – all your results will have a number, so they will not know if it is you.

- The information might also be inspected by the National Health Research Ethics Committee (NHREC), University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC) and/or the United States Food and Medicine Administration (FDA) as well as your personal doctor. Therefore, you hereby authorize me to release your medical records to the Medical Research Council, its employees or agents, domestic and foreign regulatory health authorities, the South African Medicines Control Council (MCC), the National Health Research Ethics Committee (NHREC) and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- These records will be used by them only to carry out their duties relating to this clinical study.
- Any information uncovered regarding your test results or state of health as a result of your participation in this study will be strictly confidential. You will be told about any findings of importance to your health or continued participation in this study but this information will not be given to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, I will tell you about this and that I will be giving the information to be the authorised state agency.

PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION

Please tell me below, if you want me to notify your personal doctor or your specialist that you will be taking part in this study:

- **YES**, I want you to tell my personal doctor / specialist of my participation in this study.
- **NO**, I do not want you to tell my personal doctor / specialist of my participation in this study.
- **I do not have** a personal doctor / specialist

PARTICIPANT QUESTIONS

Do you, as the participant have any questions?

YES / NO

If YES – Please describe.

INFORMED CONSENT FOR PARTICIPATION IN THE STUDY

I hereby confirm that I have been informed by the study nurse/sub-investigator..... *(FULL NAME)* about the nature, conduct, benefits and risks of clinical study titled "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels"

(PROTOCOL NUMBER 1.5)

- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) about this clinical study.
- I am aware that the results of the study, including personal details about my sex, age, date of birth, initials and diagnosis will be anonymously (my name will not be provided) processed into a study report.
- I am aware that I will need to come to the Helen Joseph clinic every second week for hearing and blood tests for 3 months.
- I am aware that I can choose to either go to my local clinic or the Helen Joseph clinic daily for my injections and I agree to do this daily.
- In view of the requirements of research, I agree that the data collected during this study can be put through a computerised system planned by the researchers involved in this study, the funders or on their behalf.
- I consent to participating in 7 sets of hearing tests in the first 3 months.
- I consent to participating in 8 sets of blood tests in these 3 months.
- I consent to give 2mls of blood 2 times in the first 3 months.
- I consent to giving 4mls of blood 6 times during the study. And another 9 mls to measure my kidney functions in the first 3 months.
- I do know that I can withdraw at any time.
- I may, at any stage, without unfairness, pull out my consent and participation in the study.
- I have had enough time to ask questions and (of my own free will) declare myself ready to participate in the study.
- I am aware that should my doctor change my medication to something other than kanamycin, I will be withdrawn from the study.

PARTICIPANT

_____

Printed Name Signature / Mark or Thumbprint Date and Time

STUDY SUB-INVESTIGATOR/ COORDINATOR

I, ..., herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

_____

Printed Name Signature Date and Time

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT (SUB-INVESTIGATOR)

_____

Printed Name Signature Date and Time

WITNESS (If applicable)

_____

Printed Name Signature Date and Time

INOMBOLO YOSHICILELO LWEMVUME ENIKEZWA EMVA KOKUTHOLA ULWAZI:

1.5

(Isibhedlela sase Helen Joseph)

ISIHLOKO SOCWANINGO: Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin isebenza kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa

ISIKHUNGO: Inyuvesi yase-Witwatersrand ibambisene ne-Sefako Makgatho Health Sciences University

IZINOMBOLO ZOCINGO (ZEZINGCINGO) NGESIKHATHI SAMAHORA OKUSEBENZA NANGEMUVA KWAMAHORA OKUSEBENZA: 082 815 8878 (Cara Hollander) kanye/noma 011 276 8968 (Dkt. Rebecca Berhanu - Ongudokotela) kanye /noma +27 11 276-8813 (Dkt. Mohammed Rassool – Umcwaningi Omkhulu – Udokotela wase Helen Joseph – Wits Health Consortium)

UMXHUMANISI WOCWANINGO: Matshediso Mkhwanazi: Inombolo yocingo esheshayo: 50017/ 076 711 2874 Matshidiso. Mkhwanazi@righttocare.org

Kulowo okunokwenzeka ukuba abambe iqhaza: *Leli fomu lemvume kungenzeka ukuthi liqukethe amagama ongawaqondisisi. Uyacelwa ukuba ubuze udokotela wocwaningo noma unesi wocwaningo noma umsebenzi wocwaningo ukuze akuchazele noma yimaphi amagama noma ulwazi ongaluqondisisi kahle. Ungakwazi ukuzigcinela* ***ikhophi elingasayiniwe lale mvume*** *ukuze ucabange ngalo noma uxoxe mayelana nalo nabomndeni wakho noma*

ISINGENISO

Sawubona, igama lami nginguCara Hollander ngingudokotela wezinzwa zokuzwa wase-University of the Witwatersrand. Ngingathanda ukuba ucabange mayelana nokuhlanganyela kulolu cwaningo lophenyo, olwaziwa ngokuthiwa "Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin isebenza kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezone-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa". Sisandukwenza okunye ukuhlola okuqinisekisa ukuthi uyafaneleka ukubamba iqhaza kulolu cwaningo.

- Ngaphambi kokuvuma ukubamba iqhaza kulolu cwaningo, kubalulekile ukuthi ufunde lezi zincazelo ezilandelayo futhi uziqondisise ezimayelana nenhloso yalolu cwaningo, izinqubo zocwaningo, izinsizakalo, ubungozi, izinto ezikwenza ungakhululeki, nezindlela zokuphepha kanye nelungelo lakho lokuhoxa kulolu cwaningo noma nini.
- Leli bhukwana lolwazi lenzelwe ukukusiza ekuthatheni isinqumo sokuthi ungathanda yini ukubamba iqhaza. Kudingeka ukuba wazi yonke into mayelana nalolu cwaningo ngaphambi kokuvuma ukubamba iqhaza kulolu cwaningo.
- Uma unemibuzo, ngizicela ungibuze.
- Akuphoqelekile ukuba ubambe iqhaza ngaphandle uma wenelisekile mayelana nazo zonke izingxenye ezibandakanyekayo.
- Awuvunyelwe ukubamba iqhaza kolunye ucwaningo lophenyo ngesikhathi usabambe iqhaza kulolu cwaningo (ngaphandle uma ngikunikile imvume ngaphambi kwalokho).
- Ngicela ungangifihleli lutho mayelana nomlando wakho wezempilo, njengoba lokho kungenza ukuba uzilimaze ngokubamba iqhaza kulolu cwaningo.
- Uma unquma ukubamba iqhaza kulolu cwaningo, uzocelwa ukuba usayine leli fomu ngenhloso yokuqinisekisa ukuthi uyaluqondisisa lolu cwaningo. Uzonikezwa ikhophi ukuba uzigcinele lona.
- Uma unodokotela wakho ongasebenzi eHelen Joseph Hospital, ngicela uxoxe naye noma umtshele mayelana nokuthi kungenzeka ubambe iqhaza kulolu cwaningo. Uma uthanda, ngingamtshela mina udokotela wakho mayelana nalokhu.

INHLOSO YALOLU CWANINGO

Ukulesi sibhedlela noma ukulo mtholampilo ngoba unesifo sofuba esibizwa ngokuthi i-Drug Resistant Tuberculosis (i-DR-TB). Ngizothanda ukuba ucabange mayelana nokubamba iqhaza kulolu cwaningo lokukala amazinga akho okuzwa ngaso sonke isikhathi usalashelwa i-DR-TB yakho. Uzonikezwa umuthi (imijovo) wokwelapha isifo sakho sofuba esimelana nemithi obizwa nge-kanamycin kanye neminye imithi, ukuze i-TB yakho ibe ngcono, okuyikho okubaluleke kakhulu. Lo muthi ozonikezwa wona unamandla amakhulu futhi unobungozi obumbalwa, obunye balobu bungozi wukulahlekelwa wukuzwa. Noma kunjalo, kudingeka ukuba uwusebenzise lo muthi ukuze uphinde

uphile kahle. Iningi labantu abasebenzisa lo muthi bazolahlekelwa wukuzwa; nakuba lokhu kuvame ukwenzeka, akwenzeki njalo. Kungaba nzima kakhulu ukukhuluma nomndeni kanye nabangane uma usungezwa ezindlebeni kanti nokusebenza kungaba nzima. Ngakho-ke, ngesikhathi kusaqhubeka lolu cwaningo, sifuna ukukala amazinga akho okuzwa izikhathi eziyisikhombisa ezinyangeni ezintathu zokuqala, ukuze siqonde kahle mayelana nokuthi yini eyenzeka ekuzweni kwakho. Emva kwalokho sizobe sesikuhlola igazi izikhathi eziyisishiyagalombili ezinyangeni ezintathu zokuqala ukuze sibheke indlela umuthi wakho wokwelapha i-DR-TB osebenza ngayo emzimbeni wakho. Ngeke siguqule imithi yakho ye-DR-TB ngokokuhlolwa kwegazi, kodwa lokhu kungasenza siqonde ukuthi kuhluke kanjani ukusebenza komuthi ebantwini abehlukene ukuze sikwazi ukuzama ukuvimbela ukulahleka kokuzwa ngomuso, usizo lwakho luzosisiza ukwelapha ezinye iziguli ezinalesi sifo esikhathini esizayo futhi lusenze sikwazi ukuqapha ukuzwa kwakho ngaso sonke isikhathi, kanyenokubheka ubudlelwane phakathi kwendlela lo muthi osebenza ngayo emzimbeni wakho kanye nokuzwa kwakho.

Ubude besikhathi socwaningo kanye nenani lababambiqhaza

Lolu cwaningo luzokwenziwa kulesi sibhedlela nasesibhedlela sase South Rand. Ngabantu abalinganiselwa kuma-80 abazobamba iqhaza kulolu cwaningo. Ababambiqhaza bazobe beneminyaka ephakathi kweyi-18 nengama-55 ubudala. Kuzodingeka ukuba usebenzise i-kanamycin yakho izinyanga ezingaphezu kwesikhathi sokubamba kwakho iqhaza kulolu cwaningo. Sizokwenza ukuhlola izinyanga ezintathu zalolu cwaningo, okuzochazwa lapha ngezansi. Lokhu kuhlola wukuhlolwa kwegazi kanye nokuhlolwa kokuzwa. Ezinyangeni ezintathu zokuqala, uzocelwa ukuba ungivakashele izikhathi eziyi-9 ngenhloso yokuzohlolwa ngesikhathi kuqhubeka lolu cwaningo. Kuzodingeka ukuba ubuyele kulo mtholampilo mayelana nalokhu kuhlola. Usuku lwanamhlanje luzobalwa njengosuku loku-1. Kwezinye izikhathi lokhu kuhlola kuzokwenziwa ngalo lolo suku lokuvakashela kwakho emtholampilo okuvamile. Kuzodingeka FUTHI ukuba uze emtholampilo nsuku zonke ukuze uzothola umjovo wakho we-kanamycin kunesi ukuze akwazi ukurekhoda isikhathi kanye nomthamo owutholayo. Uma sifuna ukushintsha umthamo wethu, singakwenza lokho ngesikhathi salokhu kuvakasha. Sizokukhokhela ama-R150 mayelana nezindleko zokugibela njalo nje uma kudingeka ukuba uze esibhedlela mayelana nokuzohlolelwa ukuzwa negazi. Lokhu kuzokwenziwa izikhathi eziyi-9, njalo esontweni lesibili. Sizobe sesikunika imali eyanele yokugibela ukuza emtholampilo nsuku zonke (kusukela ngoMsombuluko kuya ngoLwesihlanu) ngenhloso yokuzothola imijovo yakho ye-kanamycin. Ngesikhathi uza emtholampilo mayelana nokuvakasha kwakho kocwaningo “okusemthethweni” uma uzohlolelwa igazi nokuzwa sizokunika ama-R150. Uma uyisiguli esilaliswe esibhedlela, ngeke ukhokhelelwe izindleko zokugibela kuze kube uyakhishwa esibhedlela njengoba ungeke ube nesidingo sokugibela.

IZINQUBO

Uma uvuma ukubamba iqhaza kulolu cwaningo, uzobuzwa imibuzo bese wenziwa ukuhlolwa okumbalwa – okuzobe kuwukuhlolelwa ukuzwa kanye nokuhlolwa kwegazi lakho. Lokhu kuhlolwa kuzokwenziwa phezu kokunye ukuhlolwa kwakho noma naphezu kwezinye izinqubo ezingahlobene nalolu cwaningo.

Uma uvuma ukubamba iqhaza kulolu cwaningo kuzodingeka ukuba ngikubuze imibuzo embalwa namhlanje bese ngikuhlola. Bese ubuya kusasa ukuze wenze okunye ukuhlolwa kwegazi nokuhlolwa kokuzwa kokuqala

Kuzodingeka ukuba uze lapha nsuku zonke (kusukela ngoMsombuluko kuya kuLwesihlanu – hhayi ngezimpelasonto) ngenhloso yokuzothola umjovo wakho we-kanamycin. Bese kuthi njalo esontweni lesibili, kudingeke ukuba uhlolwe igazi uhlolelwe nokuzwa futhi. Lezo nsuku zizothatha isikhathi eside uma kuqhathaniswa nokuvakasha kwakho kwansuku zonke.

Inhloso yokuhlolelwa ukuzwa

Izindlebe zethu ziyizitho zomzimba ezimangalisayo ngoba ziyakwazi ukuzwa imisindo eminingi ehlukahlukene. Siyakwazi ukuzwa imisindo emincane njengomsindo owenziwa ngumshini wokugunda utshani, noma yibhasi, noma ngisho nokuconsa kwamanzi empompini. Le yimisindo ihlukahlukene, futhi inamazinga omsindo ahlukahlukene kodwa yonke le misindo iphansi. Futhi siyakwazi ukuzwa imisindo ephakeme, isibonelo izinyoni ezisho ngengila ephezulu noma ukukhala kwe-alamu yewashi.

Imisindo yenkulumo, amagama nemisho konke lokhu kuyimisindo ehlukahlukene. Isibonelo, u- /m/, u-/d/ no-/b/ kuyimisindo ephansi kodwa u-/f/, u-/s/ no-/th/ kuyimisindo ephezulu. Ukuze sizwane, kudingeka sikwazi ukuzwa imisindo eminingi ehlukahlukene, njengemisindo yenkulumo njengoba inemisindo eminingi ehlukahlukene.

Uma sesiqala sizwa imisindo ephansi yodwa, singasayizwa imisindo ephezulu, kusho ukuthi siyehluleka ukuzwa inkulumo. Ngakho, isibonelo, uma umuntu ethi ‘head’, awube usamuzwa kahle ucabange ukuthi uthi ‘bed’. Uma umuntu ethi ‘fate’, ungezwa kuphela sengathi uthi ‘ate’. Ngakho-ke ukulahlekelwa ukuzwa ngisho nasemisindweni embalwa kungenza ukuba ungakuqondi lokho okushiwo ngabangane bakho, umndeni kanye nabodokotela bakho.

Ukulahlekelwa wukuzwa kungadalwa yizinto eziningi ezihlukahlukene. Kwesinye isikhathi abantu kungenzeka bazalwe bengezwa kahle, noma kungenzeka ukungezwa kahle kudalwe ngumsindo ophezulu, wukwethuka ngokwedlulele kanye nemithi ethile. I-DR-TB yisifo esibi kakhulu futhi udinga umuthi onamandla amakhulu ukuze uphole uphinde uphile. Noma kunjalo, kwezinye izikhathi le mithi ingadala ukulahlekelwa wukuzwa, okungenza ukuba kube nzima kuwe ukuzwa nokuxhumana nabanye abantu.

Njengoba kudingeka umuthi onamandla kakhulu (i-kanamycin) ukuze uphile, kumele ukuba uwusebenzise. KODWA, lolu cwaningo luzama ukuqonda ngqo i uhlobo lokulahlekelwa wukuzwa oludalwa yilo muthi okuzokwenza ukukwelapha kangcono lokhu kulahlekelwa wukuzwa noma ukukuvikela esikhathini esiizayo.

Sidinga ukukala indlela ozwa ngayo imisindo ehlukahlukene ngesikhathi uza esibhedlela, bese kuthi emva kwalokho kube masonto onke ambalwa, ukuze sibone ukuthi kuhlala kunjalo noma kuya ngokuya kuba kubi.

<u>Izinqubo zokuhlola ukulahlekelwa wukuzwa</u>

Ukuhlolela ukuzwa akubuhlungu, futhi kunezingxenye ezimbalwa, ezimi kanje:

- I-otoscopy – Okokuqala, kuzodingeka ukuba ngibheke phakathi ezindlebeni zakho ukuze ngibone ukuthi akukho sigonogono yini, noma ezinye izinto ezindlebeni zakho, njengoba lokhu kungenzeka kube nomthelela emiphumelweni yakho. Lokhu kuzothatha cishe imizuzwana engama-20.
- Ukulawulwa kwesigonogono – Uma izindlebe zakho zivalekile ngenxa yesigonogono, ngizosikhipha ukuze singabi nomthelela kokunye ukuhlola. Ngizofaka amafutha endlebeni yakho ukuze isigonogono sakho sithambe. Ngizobe sengisebenzisa umshini ukukhipha isigonogono (ukusimunca). Ukumunca kuzothatha imizuzwana embalwa nje kuphela. Kungenzeka uzwe ubuhlungwana, kodwa akuvamile ukuba buhlungu.
- I-tympanometry (uhlobo lokuhlola okukala ukusebenza kwengxenye yendlebe ephakathi naphakathi) – ngizobe sengibeka umshini phakathi endlebeni yakho. Lo mshini othambile uzofuthela umoya endlebeni yakho. Ngeke kube buhlungu, kodwa kuzokwenza ukuba sazi ukuthi ingabe zikhona yini izifo ngaphakathi ekujuleni kwendlebe yakho, uma kukhona noma yiluphi uketshezi. Uma lukhona uketshezi, lizoba nomthelela ekuzweni kwakho kanye nasemiphumelweni yokuhlola. Lokhu kuzothatha cishe imizuzu emi-2.
- I-Distortion Product Otoacoustic Emissions – Sinamaseli ezinwedlana ekujuleni kwezindlebe zethu. Amaseli ezinwele ahlukahlukene abalulekile ekuzweni imisindo ehlukahlukene. Ngakho-ke umshini i-DPOAE ukala indlela lawa maseli ezinwele ahamba nasebenza ngayo. Sidinga ukufaka lo mshininyana othambile endlebeni yakho ukuze wenze imisindo ehlukahlukene. Kumele unganyakazi futhi uthule, lo mshni uzobe usuthatha izilinganiso zalawa maseli ezinwele. Lokhu kuzothatha cishe imizuzu emi-5 kuya kweyi-10.
- I-Pure Tone Audiometry – Sizokufaka ama-headphone. Azokhipha imisinjwana. Le misindo izoba namaphimbo ahlukahlukene. Amanye azoba phansi kanti amanye azoba phezulu. Lapho uzwa umsindo, kuzomele ucindezele inkinobho. Lokhu kuzothatha cishe imizuzu eyi-15 kuya kwengama-20.

- Uma lokhu sekwenziwe, sizobe sesikwazi ukuhlanganisa imiphumela bese siqonda kahle ukuthi yikuphi okwazi ukukuzwa. Uma sikuhlola ngesikhathi uza esibhedlela, bese sikuhlola futhi ngezikhathi ezithile, sizokwazi ukubona ukuthi ukuzwa kwakho kuyashintsha yini.

Uma ukuvuma lokhu, kuzodingeka ukuba ukwenze izikhathi eziyisi-7 ezinyangeni ezintathu zokuqala. Kungaba kusasa, bese kuba njalo esontweni lesibili ezinyangeni ezintathu ezilandelayo. Emva kwezinyanga ezintathu zalolu cwaningo, odokotela abaphathelene nemizwa yokuzwa (audiologists) balesi sibhedlela noma esibhedlela noma emtholampilo wesifunda sakho bazoqhubeka nokuqapha ukuzwa kwakho. Uma kwenzeka ulahlekelwa wukuzwa, bazoqhubeka nokukusiza ngezinsizakuzwa kanye nokunye ukulawula ukuzwa kwakho. Ngizokudlulisela kubo emva kwalolu cwaningo.

<u>Amasampula egazi</u>

Sizodinga ukukuthatha negazi. Sizodinga ukukuthatha igazi ukuze sikwazi ukulinganisa indlela umuthi (i-kanamycin) osetshenziselwa ukwelapha i-DR-TB yakho ukuthi usetshenziswa kanjani emzimbeni wakho. Sethemba ukuthi lokhu kuzosisisza ukuba sikwazi ukuqonda ukuthi yingani abantu belahlekelwa wukuzwa. Mina noma omunye unesi noma i-phlebotomist sizokuthatha igazi ukuze senze ukuhlola okudingekayo. Sizodinga ukukuthatha ama-2 ml egazi mayelana nalokho nalokho kuhlola. Kuzodingeka ukuba okungenani sikuhlole igazi kabili ngaleso naleso sikhathi (ngaphandle kokuvakasha okubili kokuqala). Amamililitha amabili cishe alingane namaconsi amabili egazi noma uhhafu wethisipuni. Ngakho-ke, kuzodingeka ukuba sikuthathe ama-4 ml egazi ngalolo nangalolo suku esikubona ngalo ukuze sikale i-kanamycin (okuzoba yigazi elingaphansana kwethisipuni). Uma uqala ukuthathwa igazi kuzobe kungemva kwamahora ambalwa uthole umjovo wakho we-DR-TB. Bese sikuthatha igazi okwesibili osukwini olulandelayo ngaphambi kokuthola umjovo wakho. Kanti kwezinye izikhathi, kuzodingeka ukuba uthathwe igazi lakho ngaphambi kokuthola umjovo, <u>futhi</u> kumele kudlule amahora ambalwa emva kokuthola umjovo. Ngakho-ke mayelana nokuvakasha ngakunye (ngaphandle kokuvakasha kwesibili lapho uhlolelwa igazi), kuzodingeka ukuba ube semtholampilo cishe amahora amane nesigamu. Kuzodingeka ukuba senze lokhu izikhathi eziyi-8 sezihlangene zonke ezinyangeni ezintathu (kusasa kuzobe kungokokuqala). Ngakho-ke sekukonke, ezinyangeni ezintathu, sizothatha inani elingama-28 ml legazi selilonke, elicishe libe ngamathisipuni amahlanu nesigamu.Ngakho-ke sizobe sithatha igazi senze nokuhlolwa kokuzwa. Futhi-ke, ukuze siqonde ukuthi umuthi unamthelela muni ezinsweni zakho, sizothanda nokuhlola ukusebenza kwezinso.

Ekuvakasheni okuthathu kokuyisishiyagalolunye, sizodinga ukukuthatha elinye igazi elingama-3 ml, ukuze sikale ukusebenza kwezinso zakho ukuze senze ushintsho olulungile lomthamo. Ngakho-ke

ngaleso sikhathi sokuvakasha lapho kuzodingeka ukuba sihlole lokhu, sizodinga amanye ama-3ml angeziwe egazi, okungaba ngaphezudlwana nje kwethisipuni. Kumahlandla amathathu sizokuthatha igazi elingama-9 ml selilonke, elingaba ngaphansana nje kwamathisipuni amabili ukwengezela ekuhlolweni kwegazi osekuchaziwe lapha ngenhla. Sizokuthatha leli gazi ngesikhathi esisodwa nesokuhlolelwa igazi mayelana ne-kanamycin – ukuze ungahlatshwa kaningi ngenalidi. Ukuthathwa kwegazi kuyingxenye yokunakekelwa kwakho okuvamile ngokwezempilo kulesi sibhedlela. Kuzodingeka ukuba sikuthathe igazi kodwa lokhu singakuhlanganisi nezinqubo ezivamile zasesibhedlela. Lokhu kungakuzizwa ubuhlungwana. Sizokuthatha igazi ngendlela efanayo naleyo esetshenziswa uma uthathwa igazi ngenhloso yokuhlolelwa kwakho igazi okuvamile. Ukuthathwa kwegazi kungakwenza uquleke, uvuvuke umthambo wegazi, uzwe ubuhlungu, uhuzuke noma wophe lapho kungene khona inalidi. Kukhona namathuba amancane okusuleleka ngesifo. Ongoti babahlengikazi odokotela noma ama-phlebotomist bazokuthatha igazi endaweni ehlanzekile ukuze baqinisekise ukuthi kuphephile.

Igazi lakho lizogcinwa ngokuphephile esibhedlela sase-Helen Joseph kuze kufike leso sikhathi selithunyelwa elabhorethri ukuze liyohlolwa. Lizothunyelwa ngaphandle kokuchitha isikhathi. Ngeke ligcinwe isikhathi esingaphezu kwesonto. Igazi lakho liyothunyelwa elabhorethri yase Sefako Makgatho Health Sciences University. Bese kuthi lelo gazi esilithathela ukukala ukusebenza kwezinso zakho lona lizothunyelwa kwenye ilabhorethri, ebizwa i-CLS. Lonke ulwazi oluqondene nawe ngqo mayelana nalokhu kuhlola namayelana nezempilo yakho jikelele kuzogcinwa kuyimfihlo efayilini ezohlala ekhabetheni ngesikhathi kuqhubeka lolu cwaningo nangesikhathi seluphothuliwe. Ulwazi oluqondene nawe ngqo ngeke kuxoxwe ngalo nomunye umuntu ongabandakanyekile kulolu cwaningo lophenyo. Uma lokhu kudingeka, sizocela imvume yakho ngaphambi kokuba kwenziwe. Lokhu sikudingela ukuqinisekisa ukuthi lonke ulwazi lurekhodwe ngendlela elungile, ngenhloso yokuqinisekisa ukuthi sihlaziya.

imiphumela ukuze sibone ukuthi lokhu kuqashwa komuthi wokwelapha (okungukushintsha imithamo yakho ye-kanamycin) kusebenzile yini.

Ukuhlolelwa ukuzwa kanye nokuhlolwa kwegazi kuzokwenziwa ngosuku lwesibili (kusasa), nangosuku lwe-15, 28, 40, 54, 68 kanye nolwama-84. Ukuhlolwa kwegazi kuzokwenziwa kusasa (ngosuku lwesi-2), ngosuku olulandelayo (usuku lwe-3), bese kwenziwa ngosuku olulodwa lokuhlolelwa kwakho ukuzwa – osukwini lwe-15, 28, 40, 54, 68 kanye nangosuku lwama-84.

Lokho nalokho kuvakasha ngenhloso yokuzohlolelwa ukuzwa kanye nokuzohlolwa igazi (hhayi lezo zinsuku eziphakathi oza ngazo uma uzojovwa), kuzothatha cishe amahora ama-5 kuya kwayi-6. Lokhu

kudalwa wukuthi sidinga ukuba silinde amahora amane nesigamu phakathi kokuhlolwa igazi okwenziwa kabili. Ngakho kungabangcono ukuba usheshe ufike ekuseni ukuze ukwazi ukubuyela emuva ntambama.

KUNGENZEKA YINI UKUTHI LEZI ZINQUBO ZINGIZWISE UBUHLUNGWANA NOMA ZINGIPHAZAMISE?

Ukuthathwa kwegazi kungakuzwisa ubuhlungwana. Igazi sizolithatha ngendlela efanayo naleyo esetshenziswayo ngesikhathi uhlolwa igazi. Ukuthathwa kwegazi kungakwenza uquleke, uvuvuke umthambo wegazi, uzwe ubuhlungu, uhuzuke noma wophe kuleyo ndawo elikhishwe kuyo. Kukhona namathuba amancane okungenwa yisifo. Igazii lakho lizothathwa ngamanesi (noma ama-phlebotomists) angongcweti ukuze uvikeleke futhi konke kuzobe kuhlanzekile ngaso sonke isikhathi. Uzothathwa isamba segazi elingama-4 ml (elingaphansana kwethisipuni) ngalokho nalokho kuvakasha kocwaningo (ngaphandle kosuku lwesi-2 nolwesi-3). Lesi yisamba esingama-28 ml egazi, okuyigazi elingacishe libe ngamathisipuni amahlanu nesigamu egazi. Uzobe usuthathwa elinye igazi elengeziwe elingama-3 ml ngosuku lwama-40, 68 nolwama-84 – isamba esengeziwe esingama-9 ml okuyigazi elingaphansana kwamathisipuni amabili. Ngakho-ke, selilonke igazi ozothathwa lona ezinyangeni ezintathu lingama-37 ml – okuyigazi elilingana cishe namathisipuni ayisi-7 nesigamu. Lokhu kuhlolelwa ukuzwa okuchaziwe lapha ngenhla ngeke kukuzwise ubuhlungu; noma kunjalo, ukukhishwa kwesigonogono kungaba buhlungu. Angeke kube nesidingo sokukhipha wonke umuntu isigonogono, futhi akuvamile ukuba buhlungu. Ukukhishwa isigonogono kuzothatha imizuzwana embalwa nje kuphela. Kanti ukuhlola sekukonke kuzothatha isikhathi sakho esicishe sibe yimizuzu engama-30 kuya kwengama-40 ngalokho nalokho kuhlolwa. Uzokwazi ngaso sonke isikhathi ukuxoxisana nonesi mayelana nemiphumela yakho nokuthi ubuze imibuzo ngaphambi nangemuva kwalokhu kuhlola. Uma uneminye imibuzo, ungathintana nami, i-audiologist.

IZINZUZO

- Inzuzo ongayithola ngokubamba kwakho iqhaza kulolu cwaningo ukuthi uzokwazi ukuqonda isimo sokuzwa kwakho ngokugcwele nokuhlobana kwakho nokusebenza kwe-kanamycin/kwe-capreomycin emzimbeni wakho
- Kungenzeka ungazuzi lutho kulolu cwaningo.
- Ukubamba kwakho iqhaza kulolu cwaningo kuzosiza ekuthuthukiseni ulwazi kwezokwelapha olungasiza ezinye iziguli ezine-DR-TB njengawe futhi ezisengcupheni yokulahlekelwa wukuzwa.

ENYE INDLELA YOKWELASHWA

- Okwamanje, ayikho enye indlela yokwelapha ngenhloso yokwehlisa amathuba okulahlekelwa wukuzwa noma yokugwema ukulahlekelwa wukuzwa okudalwa ngumuthi we-DR-TB. uma kwenzeka ulahlekelwa wukuzwa; uzodluliselwa emtholampilo wangakini ukuze ukusize uthole izinsizakuzwa.
- Ukuqapha i-kanamycin egazini lakho akuyona inqubo ejwayelekile, ayikho enye indlela yokwenza lokhu ngaphandle kokuhlola igazi okwamanje.
- I-Audiology Department kulesi sibhedlela izokwazi ukukusiza uma ukule ndawo ephakela lesi sibhedlela. Lokhu kuyingxenye yezinqubo zikahulumeni ezivamile mayelana nokuphathwa kokulahlekelwa wukuzwa. Kwesinye isikhathi izinsizakuzwa ziyaye zingasebenzi.
- Uma unquma ukungalibambi iqhaza kulolu cwaningo, uzoqhubeka nokuthola ukunakekelwa okuhle okutholakayo njengamanje okuqondene ne-DR-TB yakho kulo mtholampilo.

IZINZUZO NOBUNGOZI BENYE INDLELA YOKWELASHWA ESEZINGENI

- Njengoba njengamanje ungekho umuthi ongasiza ekuvimbeleni noma ekwehliseni amathuba okulahlekelwa wukuzwa, awukho omunye umuthi. Uma umuthi we-DR-TB udala ukulahlekelwa wukuzwa, kuyaye kungalapheki futhi akukwazi ukulungiseka. Kodwa ungayithola insizakuzwa ezokwenyusa yonke imisindo ukuze usizakale. Noma kunjalo, kwesinye isikhathi izinsizakuzwa ziyaye zingasizi ngalutho, ngoba kuyenzeka ukuthi kwesinye isikhathi ukulahlekelwa wukuzwa kuyaye kube kubi kakhulu, okwenza ukuba izinsizakuzwa zingakwazi ukukusiza. Kwezinye izikhathi izinsizakuzwa angeke zikwazi ukukusiza mayelana nokulahlekelwa wukuzwa, njengoba kwesinye isikhathi ukulahlekelwa wukuzwa kuyaye kube kubi kakhulu ngendlela yokuthi izinsizakuzwa zingabe zisakwazi ukukusiza. Ngeke sikunikeze izinsizakuzwa – iminyango yezibhedlela ye-audiology ingakwazi ukukusiza ngalokho uma ukule ndawo ephakela lezi zibhedlela, noma singakudlulisela emtholampilo noma esibhedlela esilungile esikuleyo ndawo ephakela leso sibhedlela.
- Izinzuzo zezinsizakuzwa kungenzeka zibe nemikhawulo, kodwa-ke kungenzeka zikusize uma kwenzeka ulahlekelwa wukuzwa kwakho ngenxa yokusebenzisa umuthi we-DR-TB. Izinsizakuzwa azinabo ubungozi.

NGABE ZIKHONA YINI IZEXWAYISO NOMA IMIBANDELA MAYELANA NOKUBAMBA KWAMI IQHAZA KULOLU CWANINGO

- Uma unesifo sikashukela i-Diabetes Mellitus awuvunyelwe ukubamba iqhaza kulolu cwaningo. I-Diabetes Mellitus kuyenzeka kwesinye isikhathi sibe nomthelela ekuzweni, kanti sifuna ukukala ukuzwa kwakho ngaphandle kokuthikamezeka.

- Uma uneminyaka yobudala engaphansi kweyi-18, noma uneminyaka yobudala engaphezulu kwengama-55, ngeke ukwazi ukubamba iqhaza kulolu cwaningo. Kulolu cwaningo sikala kuphela abantu abaphakathi kweminyaka yobudala eyi-18 nengama-55.
- Uma udokotela wakho eshintsha imithi yakho, ngeke usakwazi ukuqhubeka nokubamba iqhaza kulolu cwaningo.
- Uma kade ungakwazi ukuphila ngaphandle kwanoma yisiphi isidakamizwa futhi unomlando wokusebenzisa budedengu izidakamizwa notshwala, ngeke ukwazi ukubamba iqhaza kulolu cwaningo uma lokhu kungaba nomthelela ekulandeleni kwakho imiyalelo yezinqubo zokuhlola. Isinqumo mayelana nalokhu sizothathwa abacwaningi ababandakanyekayo.

AMALUNGELO NJENGOMBAMBIQHAZA KULOLU CWANINGO

Ukuzithandela

Ukubamba kwakho iqhaza kulolu cwaningo kungukuzithandela kwakho futhi unokuzikhethela ukuthi uyafuna noma awufuni ukubamba iqhaza kulolu cwaningo. Futhi uyakwazi ukuyeka ukubamba iqhaza kulolu cwaningo noma nini ngaphandle kokunikeza isizathu. Uma unquma ukungalibambi iqhaza kulolu cwaningo, noma unquma ukuyeka ukubamba iqhaza ngesikhathi kusaqhubeka lolu cwaningo, uzoqhubeka nokuthola unakekelo lwezempilo kulesi sibhedlela, futhi ngeke lokhu kuthinteke.

Okusha okutholwayo

Ngizokunikeza noma yiluphi ulwazi olusha enginalo ngesikhathi kusaqhubeka lolu cwaningo, okungenzeka lukwenze ushintshe umqondo wakho wokufisa ukuqhubeka ukulolu cwaningo.

Ukuhoxa

Ukuhoxa kwakho noma ukuyeka ukubamba iqhaza kulolu cwaningo ngeke kuthinte ukunakekelwa kwakho ngokwezempilo. Nginelungelo lokukuhoxisa kulolu cwaningo uma lokho kuzosiza wena. Uma udokotela wakho eshintsha imithi yakho ye-DR-TB futhi ungasasebenzisi i-kanamycin, ngeke usakwazi ukuqhubeka nokubamba iqhaza kulolu cwaningo. Uma unganikezanga ulwazi olulungile nolwethembekile mayelana nomlando wakho wezempilo, noma ungalandelanga imithetho yalolu cwaningo, ngizokukhipha kulolu cwaningo noma nini.

UKUNAKEKELWA NGAPHANSI KWEZIMO EZIPHUTHUMAYO KANYE NOKUNGENISWA ESIBHEDLELA

Uma udinga usizo oluphuthumayo noma nini ngesikhathi kuqhubeka lolu cwaningo, uyacelwa ukuba ushayele uDkt Mohammed Rassool ucingo kule nombolo: 011 276-8813 noma kule nombolo: 027 83 415 8967 noma ushayele uDkt Rebecca Berhanu kule nombolo: 011276 8968 noma kule nombolo: 072 717 9159.

AMALUNGISELELO EZEZIMALI

- Abaxhasi balolu cwaningo bazokhokhela konke ukuhlola okuzokwenziwa kulolu cwaningo.
- Wena nabe-medical aid yakho (uma unayo) angeke kudingeke ukuba nikhokhele noma yimiphi imithi yalolu cwaningo noma izinqubo zalolu cwaningo, konke lokhu kuxhaswe yizinhlangano zalolu cwaningo.
- Ngesikhathi uvakashela esibhedlela ngokwalolu cwaningo njalo esontweni lesibili (ukuze uhlolelwe ukuzwa kanye nokuhlolwa igazi) uzonikezwa ama-R150 okugibela. Ngeke ukhokhelwe ngokubamba iqhaza, kodwa uzokhokhelwa kuphela imali yokugibela neyokudla okulula. Uma uza nsuku zonke ukuzothola umjovo wakho kanye noshintsho lomthamo okungenzeka lwenziwe, uzonikezwa imali eyanele yokugibela (kube kubhekwe indawo ohlala kuyo). Lokhu kuzokwenziwa kuphela ezinyangeni ezintathu zokuqala. Emva kwalezi zinyanga ezintathu, uzothola umjovo wakho emtholampilo oseduze nawe, kanti ayikho imali yokugibela ozonikezwa yona.

IMVUME YENKAMBISO ELUNGILE

- Iphrothokholi yalolu cwaningo lwezokwelapha isinikeziwe ku-University of the Witwatersrand, **Human Research Ethics Committee (HREC)** kantileli komidi isinikezele ngemvume ebhalwe phansi.
- Lolu cwaningo lulandela imihlahlandlela ye-**Declaration of Helsinki** (egcine ukubuyekezwa: ngo-Okthoba 2013), ebhekele izincomo mayelana nodokotela abenza ucwaningo lwezokwelapha olubandakanya ababambiqhaza okungabantu. Uma ufisa ukuthola ikhopho yale migomo, ngicela ungazise ukuze ngikutholele lona.
- Lolu cwaningo lukhokhelwe yinhlangano yocwaningo (i-South African Medical Research Council). Akukho nzuzo engiyibhekile yemali noma mina angeke ngizuze ngalutho kule nhlangano futhi ayikho ingcindezi engiyithola kule nhlangano noma angichemile nayo.

UMSHWALENSE

Bonke odokotela abangabacwaningi kulolu cwaningo banomshuwalense.

Umcwaningi omkhulu nodokotela banomshuwalense we-MPS ukuba benze izinqubo uma nje:

- Behlonipha izinqubo zephrothokholi yocwaningo.
- Behambisana nemithetho yesigungu esilawula imithi neye-University of the Witwatersrand Research Ethic Committee.
- Bephatha imithi yocwaningo ngokwephrothokholi nokugguqulwa kwayo kanye nemibhalo ehlobene.

Lokhu kuvikela akuhlosile futhi akuthathi indawo yomshuwalense yokungasebenzi komuntu ngendlela efanele. Sicela uqaphele ukuthi uma une-policy yomshuwalense wempilo kufanele utthole noma inkampani yomshuwalense idinga ukwaziswa mayelana nokubamba kwakho iqhaza ocwaningweni. Ngokolunye ulwazi, lokhu akufanele kuphazamise noma iyiphi enye i-policy yomshuwalense wempilo onayo. Kodwa kubalulekile ukuthi ubhekisise ngoba kuyenzeka izinkampani zingafani.

UMTHOMBO WOKUTHOLA OLUNYE ULWAZI

Ngesikhathi kusaqhubeka lolu cwaningo, uzonakekelwa ngabasebenzi baseHelen Joseph Hospital. Noma nini uma ufisa ukubuza eminye imibuzo ehlobene nalolu cwaningo, ngicela ungithinte noma uthinte unesi wocwaningo/umdidiyeli wocwaningo osemsebenzini ngalesi sikhathi esibhedlela.

Amalungu ocwaningo ongaxhumana nawo:

- ✓ UCara Hollander – 082 815 8878 (oyi-Audiologist)
- ✓ UDkt. Karin Joubert – 011 717 4561 (oyi-Audiologist)
- ✓ UDkt. Natalie Schellack – 012 521 3286 (onguSokhemisi)
- ✓ UDkt. Rebbeca Berhanu – 011 276 8968 (ongudokotela)
- ✓ UDkt. Mohammed Rassool –011 276-8813 (ongudokotela Nomphenyi Omkhulu)

- Uma ufuna noma yiluphi ulwazi oluthe xaxa mayelana **namalungelo akho njengombambiqahaza ocwaningweni, noma uma ufuna ukudlulisa ukukhalaza mayelana nalolu cwaningo lophenyo**, ungaxhumana noSlz Cleaton-Jones, uSihlalo we-University of the Witwatersrand, Human Research Ethics Committee (HREC), okuyikomidi elizimele elisiza ekuvikelweni kwamalungelo ababambiqhaza ocwaningweni kule nombolo: (011) 717 2301.
- Mayelana **nolwazi olumayelana nocwaningo,** ungashayela umdidiyeli Wocwaningo – uCara Hollander wase-University of the Witwatersrand kule nombolo: 082 815 8878.

UBUMFIHLO

- Lonke ulwazi esiluqoqa ngesikhathi kuqhubeka lolu cwaningo, olubandakanya amarekhodi asesibhedlela, ulwazi oluqondene nomuntu ngqo kanye nolwazi olumayelana nocwaningo luzogcinwa luyimfihlo. Ulwazi lwakho luzobonwa ngamalungu eqembu locwaningo kuphela, kanye nosokotela bakho kanye namanesi. Noma yiluphi ulwazi oluzobe lubhalwe kumajenali esayensi noma nanoma yikuphi okushicilelwayo ngeke kube negama lakho kukho.

- Sizofaka amakhodi ahlukahlukene olwazini lwakho locwaningo. Ngakho-ke uma imiphumela yakho ibuyekezwa, izobe inekhodi kuphela. Igama lakho, inombolo yakho kamazisi noma nanoma yimaphi amanye amanothi okungenzeka akuhlonze ngeke kufakwe kulawo mabhukwana, ukuze kuqinisekiswe ukuthi konke kuyimfihlo.
- Lolu lwazi luzobuyekezwa ngabaphathiswa abagunyaziwe be-University of the Witwatersrand kanye nabase- Sefako Makgatho Health Sciences University kanye namalungu avela kubaxhasi (i-Medical Research Council). Abacwaningimabhuku be-Wits Health Consortium bavunyelwe ukubheka eminye imiphumela ngesikhathi behlola ngenhloso yokuqinisekisa ukuthi konke kwenziwe ngokulandela amazinga amahle. Nakuba kunjalo, akusiyena wonke umuntu ozofinyelela egameni lakho – yonke imiphumela yakho izoba nenombolo, okuzokwenza ukuba bangazi ukuthi nguwe.
- Kungenzeka futhi ukuthi ulwazi luhlolwe ngabe-National Health Research Ethics Committee (NHREC), yi-University of the Witwatersrand, Human Research Ethics Committee (HREC), yi-South African Medicines Control Council (MCC) kanye/noma yi-United States Food and Medicine Administration (FDA) kanye nodokotela wakho. Ngakho-ke lapha uyangigunyaza ukuthi ngikhulule amarekhodi akho ezokwelapha ngiwanike i-Medical Research Council, abasebenzi bayo noma ama-ejenti ayo, abasemagunyeni kwezokulawulwa kwezempilo bakuleli lizwe nabakwamanye amazwe, i-South African Medicines Control Council) i-MCC), i-National Health Research Ethics Committee (NHREC) kanye ne-University of the Witwatersrand, Human Research Ethics Committee (HREC).
- Lawa marekhodi azosetshenziswa yibo kuphela ekwenzeni imisebenzi yabo ehlobene nalolu cwaningo lwezokwelapha.
- Noma yiluphi ulwazi oludaluliwe mayelana nemiphumela yokuhlolwa kwakho noma isimo sakho sempilo ngenxa yokubamba kwakho iqhaza kulolu cwaningo luzohlala luyimfihlo. Uzotshelwa mayelana nanoma yikuphi okutholakele okubalulekile mayelana nezempilo yakho noma okubalulekile mayelana nokuqhubeka kwakho ukubamba iqhaza kulolu cwaningo, kodwa lolu lwazi ngeke lunikezwe noma yimuphi omunye umuntu phezu kwalabo abashiwo lapha ngenhla ngaphandle kwemvume yakho ebhalwe phansi. Esimweni lapho lo mthetho ungeke usebenze khona yikulezo zimo ezimayelana nezifo ezithathelanayo lapho umthetho okhona udinga ukuba kwaziswe aboMnyango Wezempilo. Uma kuba nesimo esinjalo, ngiyokwazisa ngaso ngiphinde ngikwazise futhi ukuthi lolo lwazi ngizoludlulisela kwi-ejenti kahulumeni egunyaziwe.

UKUKHETHA UKUBA KWAZISWE UDOKOTELA WAKHO/UNGOTIWAKHO

Ngicela ungitshele lapha ngezansi uma ufuna ukuba ngazise udokotela wakho noma isipeshalisti sakho mayelana nokuthi uzobamba iqhaza kulolu cwaningo:

- **YEBO**, ngifuna wena utshele udokotela wami noma isipeshalisti sami ngokubamba iqhaza kulolu cwaningo.
- CHA, angifuni ukuthi wena utshele udokotela wami noma isipeshalisti sami ngokubamba iqhaza kulolu cwaningo.
- Anginaye udokotela/isipeshalisti okungesami

IMIBUZO YOMBAMBIQHAZA

Ingabe unayo imibuzo njengombambiqhaza?

YEBO / CHA

Uma impendulo yakho kunguYEBO – Sicela uchaze.

IMVUME ETHATHWA EMVA KOKUNIKEZWA ULWAZI MAYELANA NOKUBAMBA IQHAZA KULOLU CWANINGO

Ngiyaqinisekisa lapha ukuthi unesi wocwaningo, ... (*IGAMA NGOKUGCWELE)* unginikezile ulwazi mayelana nesimo, ukuziphatha, izinsizakalo nobungozi obumayelana nalolu cwaningo lwezokwelapha olusihloko esithi “Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin isebenza kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa” (INOMBOLO YEPHROTHOKHOLI 1.5).

- Futhi ngilutholile lolu lwazi olubhalwe lapha ngenhla, ngalufunda ngaluqonda (Ibhukwana Lolwazi Lombambiqhaza kanye Nemvume Enikezwa Emva Kokunikezelwa Kolwazi) mayelana nalolu cwaningo lwezokwelapha.
- Ngiyazi ukuthi imiphumela yalolu cwaningo, okubandakanya imininingwane eqondene nomuntu ngqo emayelana nobulili bami, iminyaka yobudala, usuku lwami lokuzalwa, iziqalomagama kanye nokuhlonzwa kwesifo esithile kuzofakwa embikweni walolu cwaningo ngaphandle kokwaziswa ukuthi ngekabani (igama lami ngeke lidalulwe).
- Ngiyazi ukuthi kumele ngize emtholampilo wase Helen Joseph njalo esontweni lesibili enyangeni ukuze ngenze ukuhlolwa kokuzwa nokwegazi izinyanga ezintathu.
- Ngiyazi ukuthi ngingakhetha ukuya emtholampilo wendawo engihlala kuyo noma emtholampilo waseHelen Joseph nsukuzonke ukuze ngijove, futhi ngiyavuma ukwenza lokhu nsukuzonke.

- Ngokubhekelela izidingo zalolu cwaningo, ngiyavuma ukuthi imininingwane eqoqwe ngesikhathi kuqhubeka lolu cwaningo ifakwe ohlelweni lwekhompyutha oluhlelwe ngabacwaningi ababandakanyeka kulolu cwaningo, abaxhasi noma egameni labo.
- Ngiyavuma ukubamba iqhaza emasethini ayisi-7 okuhlolelwa ukuzwa ezinyangeni ezintathu zokuqala.
- Ngiyavuma ukubamba iqhaza emasethini ayisishiyagalombili okuhlolwa igazi kulezi zinyanga ezintathu.
- Ngiyavuma ukunikezela ngegazi elingama-2ml amahlandla amabili ezinyangeni ezintathu zokuqala.
- Ngiyavuma ukunikezela ngegazi elingama-4 ml amahlandla ayisithupha ngesikhathi kuqhubeka lolu cwaningo. Kanye nelinye elingama-9 ml ukuze kukalwe ukusebenza kwezinso zami ezinyangeni ezintathu zokuqala.
- Ngiyazi ukuthi ngiyakwazi ukuhoxa noma nini.
- Ngingakwazi, kunoma yisiphi isigaba, ngaphandle kokuphathwa ngendlela engafanele, ukuhoxisa imvume yami kanye nokubamba kwami iqhaza ocwaningweni.
- Ngibe nesikhathi esanele sokubuza imibuzo futhi ngiyazisholo mina (ngokuzithandela) ukuthi ngikulungele ukubamba iqhaza kulolu cwaningo.
- Ngiyazi ukuthi uma kwenzeka udokotela wami eshintsha imithi yami enginika eminye ngaphandle kwe-kanamycin/kwe-capreomycin, ngizohoxiswa kulolu cwaningo.

UMBAMBIQHAZA

Igama elibhaliwe	Isiginisha/Uphawu noma Umaka wesithupha	Usuku Nesikhathi

UMCWANINGI OMNCANE/UMXHUMANISI

Mina, ..., ngiyaqinisekisa lapha ukuthi lo mbambiqhaza ongenhla unikeziwe ulwazi olugcwele mayelana nesimo, ukuziphatha nobungozi mayelana nalolu cwaningo olungenhla.

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

UMHUMUSHI / OMUNYE UMUNTU OCHAZA IMVUME EMVA KOKUNIKEZELWA KOLWAZI (UMCWANINGI OMNCANE)

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

UFAKAZI (uma ekhona)

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

NOMORO YA VERSION YA TUMELLO E BONTSHANG KUTLWISISO:1.5

(Sepetlele sa Helen Joseph)

SEHLOOHO SA PHUPUTSO: Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng ditekanyo tsa ho utlwa ditsebeng

INSTITJHUSHENE: Yunivesithi ya Witwatersrand tshebedisanong le Sefako Makgatho Health Sciences University

(LI)NOMORO TSA MOHALA TSA LIHORA TSA MOTSHEHARE LE KA MORA

TSHEBETSO: 082 815 8878 (Cara Hollander) le/kapa 011 276 8968 (Ngaka Rebecca Berhanu - Ngaka) le/kapa +27 11 276-8813 (Ngaka Mohammed Rassool – Mofuputsi ya ka Sehloohong – Ngaka mane Helen Joseph – Wits Health Consortium)

MOHOKAHANYI EA PHUPUTSO: Matshediso Mkhwanazi: speed dial: 076 711 2874/ Matshidiso.Mkhwanazi@righttocare.org

Motho eo e ka bang Monkakarolo: *Foromo ena ya tumello e ka ba le mantswe ao o sa a utlwisiseng. Ka kopo kopa ngaka ya phuputso/mooki kapa moifo wa phuputso ho o hlalosetsa mantswe afe kapa afe ao o sa a utlwisiseng ka ho hlakileng. O ka boloka* ***kopi e sa saenwang yatumello ena*** *ya foromo ena ho nahana ka yona kapa ho buisana ka yona le lelapa kapa metswalle* ***pele o etsa qeto ya hao.***

SELELEKELA

Dumela, lebitso la ka ke Cara Hollander mme ke ngaka ya tlhahlobo ya kutlo ditsebeng ho tswa Yunivesithing ya Witwatersrand. Ke lakatsa ho o ***mema*** hore o nahane ka ho kena phuputsong, e bitswang "Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng tsa ditekanyo tsa ho utlwa ditsebeng". Re entse diteko tse itseng ho netefatsa hore o a tshwaneleha bakeng sa ho nka karolo phuputsong ena.

1. Pele o dumela ho nka karolo phuputsong ena, ho bohlokwa hore o bale le ho utlwisisa ditlhaloso tse latelang mabapi le phuputso, mekgwatshebetso ya phuputso, melemo, dikotsi, dikarolo tse bakang makukuno, le ditemoso hammoho le tokelo ya hao ya ho ikgula phuputsong ka nako efe kapa efe.

2. Bukana ena ya tlhahisoleseding e o thusa ho etsa qeto haeba o lakatsa ho nka karolo. Ho hlokeha hore o utlwisise ntho e nngwe le e nngwe mabapi le phuputso pele o dumela ho nka karolo phuputsong ena.

3. Haeba o na le dipotso dife kapa dife, ka kopo mpotse.

4. Ha o a tshwanela ho dumela ho nka karolo ntle le haeba o o thabela ho dikarolo tsohle tse amehang.

5. O ke ke wa nka karolo phuputsong e nngwe nakong eo o nkang karolo phuputsong ena (ntle le haeba ke dumella sena pele).

6. Ka kopo bua le nna o sa pate letho mabapi le nalane ya hao ya bophelo bo botle, hobane ho seng jwalo o ka ipeha kotsing haeba o nka karolo phuputsong ena.

7. Haeba o etsa qeto ya ho nka karolo phuputsong ena, o tla kotjwa hore o saene foromo ena ho netefatsa hore o utlwisisa phuputso. O tla fuwa kopi ya yona ho e boloka.

8. Haeba o na le ngaka ya hao kantle ho sepetlele sena, ka kopo buisana le yena kapa o mmolelle hore ho na le kgonahalo ya hore o nke karolo phuputsong ena. Haeba o lakatsa, nka bolella ngaka ya hao mabapi le sena.

SEPHEO SA PHUPUTSO

O sepetleng/tliliniking ena hobane o na le Lefuba le Lwantshang Moriana (DR-TB). Ke lakatsa hore o nahane ka ho nka karolo phuputso ho lekanya ditekanyo tsa kutlo ya hao nakong yohle ya karolo ya hao ya DR-TB. O tla amohela moriana (diente) ho alafa lefuba la hao le lwantshang moriana o bitswang kanamycin hammoho le meriana e meng, e le hore o ka ba betere lefung la hao la TB, e leng taba ya bohlokwa haholo. Moriana oo o tlang ho o fumana o matla haholo, mme o na le dikotsi tse mmalwa mme e nngwe ya tsona ke ho lahlehelwa ke ho utlwa ditsebeng. Le ha ho le jwalo, o tshwanetse ho sebedisa moriana ona e le hore o ikutlwe o le betere hape. Batho ba bangata ba sebedisang moriana ona ba tla lahlehelwa ke ho utlwa ditsebeng; empa, le hoja sena se etsahala kgafetsa, ha se etsahele kamehla. Ho ka ba thata haholo ho bua le lelapa le metswalle ha o lahlehetswe ke ho utlwa ditsebeng mme hape ho ka ba thata ho sebetsa. Ka lebaka lena, nakong ya phuputso ena, re lakatsa ho lekanya ho utlwa ditsebeng ka makgetlo a 7 dikgweding tsa pele tse tharo, e le hore re ka utlwisisa hantle hore na ho etsahalang ka ho utlwa ha hao ditsebeng. Mme re tla lakatsa ho etsa diteko tsa madi ka makgetlo a 8 dikgweding tsa pele tse 3, e le hore re ka sheba kamoo moriana wa hao bakeng sa DR-TB ya hao o sebetsang kateng mmeleng wa hao. Re ke ke ra fetola moriana wa hao wa DR-TB ho ya ka diteko tsa madi, empa sena re tla re dumella ho utlwisisa kamoo moriana o sebetsang ka ho fapaneng kateng bathong ba fapaneng, ka lebaka lena re ka leka ka tshepo le ho thibela tahlehelo ya kutlo ditsebeng nakong e tlang. Thuso ya hao e tla re thusa ho alafa bakuli

ba bang nakong e tlang ba nang le lefu lena mme hape ho tla re dumella ho beha leihlo ho utlwa ha hao ditsebeng nako ng yohle ya phuputso, le ho sheba kamano pakeng tsa kamoo moriana o sebediswang kateng ke mmele wa hao le kamoo o utlwang kateng ditsebeng.

NAKO YA PHUPUTSO LE PALO YA BANKAKAROLO

Phuputso e tla etsetswa sepetleng sena hammoho le Sepetleleng sa South Rand. Batho ba ka bang 80 ba tla nka karolo phuputsong ena. Bankakarolo ba tla ba pakeng tsa dilemo tse 18 le 55 ka boholo. Ho tla hlokeha hore o sebedise kanamycin ya hao ka dikgwedi tse fetang tseo o tla nka karolo ka tsona phuputsong ena. Re tla etsa diteko ka dikgwedi tse tharo bakeng sa phuputso ena, sena se tla hlaloswa mona ka tlase. Diteko tsena ke diteko tsa madi le diteko tsa ho utlwa ditsebeng. Dikgweding tsa pele tse 3, o tla kotjwa hore o nketele ka makgetlo a 9 bakeng sa diteko nakong ya phuputso. Re tla hloka hore o kgutlele tliliniking bakeng sa diteko tsena tsohle. Kajeno e tla balwa e le letsatsi 1. Ka dinako tse ding e tla ba ka letsatsi le tshwanang le la diketelo tsa hao tse tlwaelehileng tliliniking. HAPE ho tla hlokeha hore o tle tliliniking letsatsi le leng le le leng ho fumana ente ya hao ya kanamycin ho tswa ho mooki e le hore a ka ngola nako le tekanyo ya moriana eo o e fuwang. Haeba o batla ho fetola tekanyo ya hao ya moriana, re ka etsa sena nakong ya diketelo tsena. Re tla o neha R150 bakeng sa ditjeo tsa ho palama lekgetlo le leng le le leng ha ho hlokeha hore o tle sepetlele bakeng sa diteko tsa ho utlwa le diteko tsa madi. E tla ba ka makgetlo a 9, bekeng e nngwe le e nngwe ya bobedi. Haeba o le mokudi ya robaditsweng sepetlele, o ke ke wa leshwa bakeng sa ho palama, ho fihlela o ntshwa sepetlele, ka hobane o ke ke wa hloka tjhelete ya ho palama.Jwale, re tla o neha tjhelete e lekaneng bakeng sa ho palama ho tloha tliliniking letsatsi le leng le le leng (ho tloha ka Mantaha ho fihla ka Labohlano) ho fumana diente tsa hao tsa kanamycin. Ha o tla tliliniking bakeng sa diketelo tsa 'semolao' tsa phuputso, le ha o etswa diteko tsa ho utlwa ditsebeng le diteko tsa madi re tla o neha R150. O ke ke wa fumana tjhelete e eketsehileng ya ho palama eo o e fumanang letsatsi le le letsatsi bakeng sa diente tsa hao matsatsing ao o fumanang R150.

MEKGWATSHEBETSO

Haeba o dumela ho nka karolo phuputsong ena, o tla botswa dipotso mme ho tla hlokeha hore o etse diteko tse mmalwa – e tla ba diteko tsa ho utlwa le diteko tsa madi. Ho tla hlokeha hore diteko tsena di etswe ho phaella ditekong tse ding tsa hao/mekgwatshebetso e sa amaneng le phuputso.

Haeba o dumela ho nka karolo phuputsong ena le ho fana ka tumello, ho tla hlokeha hore ke o botse dipotso tse itseng kajeno le ho o hlahloba. Mme, ho hlokeha hore o kgutle hosasane hape bakeng sa diteko tsa madi a hao le diteko tsa pele tsa ho utlwa.

Ho tla hlokeha hore o tle letsatsi le leng le le leng (ho tloha ka Mantaha ho fihlela ka Labohlano - e seng mafelong a beke) ho fumana ente ya hao ya kanamycin. Hape re tla etsa diphetoho tekanyong ya hao ya moriana haeba ho hlokeha. Mme, bekeng e nngwe le e nngwe ya bobedi, ho tla hlokeha hore o etse diteko tsa madi le diteko tsa ho utlwa. Matsatsi ana a tla nka nako e telele ho feta diketelo tsa hao tsa kamehla.

Sepheo sa diteko tsa ho utlwa

Ditsebe tsa rona ke ditho tse hlollang ka hobane di ka kgona ho utlwa diphitjhi (pitch) tse mengata tse fapaneng. Re kgona ho utlwa phitjhi e tlase e jwaloka ya motjhini o kutang jwang, kapa bese, kapa esita le wa pompo e dutlang. Ena ke medumo e fapaneng, mme e na le ditekanyo tse fapaneng tsa modumo, empa kaofela e na le diphitjhi tse tlase. Hape re kgona ho utlwa phitjhi e phahameng, ka mohlala, ho lla ha dinonyana kapa ho lla ha alamo ya tshupanako.

Modumo wa puo, mantswe le dipolelo kaofela e na le diphitjhi tse fapaneng. Ka mohlala /m/, /d/ le /b/ ke medumo e tlase athe /f/, /s/ le /th/ ke diphitjhi tse phahameng. E le hore re utlwisisane, ho hlokeha hore re kgone ho utlwa di-frequency tse ngata tse fapaneng kapa diphitjhi, ka hobane medumo e jwalo ya puo e na le diphitjhi tse ngata tse fapaneng.

Ha re qala ho utlwa feela diphitjhi tse tlase, mme e seng diphitjhi tse phahameng, re qala ho ba le bothata ba ho utlwisisa puo. Ka mohlala, ha motho a re ‘head’, o ka utlwa hampe, mme o utlwe ‘bed’. Haeba motho a re ‘fate’, o ka utlwa ‘ate’. Ka lebaka lena tahlehelo ya ho utlwa esita le di-frequency tse mmalwa e tla etsa hore ho be thata ho utlwisisa metswalle, lelapa le dingaka.

Dintho tse ngata tse fapaneng di ka baka tahlehelo ya ho utlwa. Ka dinako tse ding batho ba belehwa ba na le tahlehelo ya ho utlwa, kapa e ka bakwa ke lerata le phahameng, trauma le meriana e meng. DR-TB ke lefu le totileng, mme o hloka moriana o matla haholo hore o hlaphohelwe le ho phela. Le ha ho le jwalo, ka dinako tse ding, meriana ena e ka baka tahlehelo ya kutlo, mme e ka etsa hore o be thata ho utlwa le ho buisana le ba bang.

Ka hobane moriana o matla (kanamycin) o hlokeha hore o phele, o tshwanetse ho o sebedisa. EMPA phuputso ena e leka ho utlwisisa hantle-ntle mofuta wa tahlehelo ya kutlo o bakwang ke moriana bakeng sa ho dumella kalafo e molemo haholwanyane kapa thibelo ya yona nakong e tlang. Ho hlokahala hore re lekanye kamoo o utlwang medumo kaofela e fapaneng le diphitjhi tsa modumo ha o tla sepetlele, mme ka dibeke tse ding le tse ding tse mmalwa, ho bona haeba boemo bo dula bo tshwana, kapa bo mpefala.

Mekgwatshebetso ya teko ya kutlo ditsebeng

Teko ya kutlo ditsebeng ha e bohloko, ho na le dikarolo tse mmalwa, jwaloka tse latelang:

- Otoscopy – Pele, ho hlokeha hore ke shebe hara ditsebe tsa hao ka kganya ho bona haeba ho na le dikonokono dife kapa dife ditsebeng, kapa dintho tse ding ditsebeng tsa hao, hobane sena se ka ama diphetho tsa hao. Sena se tla nka hoo e ka bang metsotswana e 20.
- Cerumen management – Haeba ditsebe tsa hao di thibane ka lebaka la dikonokono, ke tla di ntsha e le hore di se ame diteko tse ding tsa hao. Ke tla tshela oli e itseng tsebeng ya hao ho etsa hore dikonokono di be bonolo. E be ke sebedisa motjhini ho hula dikonokono. Kgulo ena e tla nka feela metsotswana e mmallwa. Ho ka utlwisisa bohloko hanyenyane, empa ha se ka dinako tsohle ho utlwisang bohloko.
- Tympanometry – E be ke kenya motjhini tsebeng ya hao. Ke nub e bonolo mme e tla pompela moya o itseng ka tsebeng ya hao. Ho ke ke ha o utlwisa bohloko, empa ho tla re thusa ho tseba haeba ho na le ditshwaetso dife kapa dife hara tsebe ya hao, le haeba ho na le mokedikedi ofe kapa ofe. Haeba ho na le mokedikedi, sena se tla ama ho utlwa ha hao, le ho ama diphetho tsa teko ya kutlo. Sena se tla nka hoo e ka bang metsotso e 2.
- Distortion Product Otoacoustic Emissions (DPOAE) – Re na le disele tse nyenyane tsa moriri hare-hare ditsebeng tsa rona. Disele tse fapaneng tsa moriri di bohlokwa bakeng sa ho utlwa diphitjhi tse fapaneng. Ka lebaka lena, motjhini wa DPOAE o lekanya kamora disele tsena tsa moriri di sisinyehang kateng le ho sebetsa. Ho hlokahala hore re kenye nub e bonolo tsebeng ya hao, mme e tla etsa medumo e fapaneng. O tshwanetse ho dula o sa sisinyehe mme o kgutsitse, mme motjhini o tla nka ditekanyo tsa disele tsena tsa moriri. Sena se tla nka hoo e ka bang metsotso e 5 ho isa ho e 10.
- Pure Tone Audiometry – Re tla o rwesa di-headphone. Di tla ntsha medumo e bonolo haholo. Medumo e tla ba le diphitjhi tse fapaneng. Tse ding di tla ba tlase, mme tse ding di tla ba hodimo. Nako le nako ha o utlwa modumo, o tshwanetse ho tobetsa konopo. Sena se tla nka hoo e ka bang metsotso e 15 ho isa ho e 20.

Hang ha sena se entswe, re tla kgona ho bokella diphetho tsa hao hammoho le ho utlwisisa hantle seo o se utlwang ditsebeng. Haeba re etsa teko ena nakong eo o tlang sepetlele, mme re e etsa hape ka dinako tse itseng dipakeng, re tla kgona ho bona haeba kutlo ya hae e fetoha.

Haeba o dumela sena, ho tla hlokeha hore o etse sena ka makgetlo a 7 dikgweding tsa pele tse 3. E tla ba hosasane, le bekeng e nngwe le e nngwe ya bobedi bakeng sa dikgwedi tse 3 tse latelang.

Ka mora dikgwedi tse 3 tsa phuputso, kutlo ya hao e tla tswela pele e behilwe leihlo ke dingaka tse hlahlobang kutlo ditseng sepetleleng sena kapa tliliniking e leng sebakeng sa lona. Haeba o lahlehelwa ke kutlo, dingaka tsena di tla tswela pele ho o thusa ka disebediswa tse thusang ho utlwa le tlhokomelo e tswelang pele. Ke tla o romela ho tsona ka mora phuputso.

Sampole ya Madi

Ho hlokeha hore re nke madi. Ho hlokeha hore re nke madi e le hore re ka lekanya kamoo kalafo ya (kanamycin) e sebediswang kateng mmeleng wa hao. Re tshepa hore sena se tla re thusa ho utlwisisa hore na ke hobaneng ha batho ba lahlehelwa ke kutlo ditsebeng. Nna, kapa mooki e mong kapa setsebi se hulang madi bakeng sa phuputso re tla nka madi ho wena e le hore re ka etsa diteko tse hlokehang. Ho hlokeha hore re nke 2 ml tsa madi bakeng sa teko ka nngwe. Ho tla hlokeha hore bonyane o be le diteko tse 2 tsa madi lekgetlo ka leng (ntle le diketelong tse 2 tsa pele). 2 ml e ka ba marothodi a 2 a madi kapa halofo ya thispuni. Ka lebaka lena, re hloka 4ml tsa madi letsatsi ka leng ha re o bona e le hore re lekanye kanamycin (ka tlase ho thispuni e le nngwe ya madi). Lekgetlo la pele e tla ba dihora tse mmalwa ka mora ho fumana ente ya hao ya DR-TB. Ka mora moo, lekgetlong la bobedi le tla latelwa ke letsatsi pele o fumana ente ya hao. Mme makgetlong a mang, ho tla hlokeha hore ho nkuwe madi a hao pele o hlajwa ente, le dihora tse mmalwa ka mora ho hlajwa ka ente ya hao. Ka lebaka lena, bakeng sa ketelo ka nngwe (ntle le ketelong ya bobedi ha ho etswa diteko tsa madi), ho hlokeha hore o be tliliniking ka dihora tse 4.5 bonyane. Ho tla hlokeha hore re etse sena ka makgetlo a 8 kaofela dikgweding tse 3 (hosasane e tla ba lekgetlo la pele). Ka hoo, dikgweding tse 3, re tla nka kakaretso ya 28 ml ya madi, hoo e ka bang dithispuni tse 5 le halofo. Haeba o le sehlopheng se fuputswang, re tla etsa diphetoho tekanyong ya moriana kanamycin enteng ya hao eo o e hlajwang letsatsi le letsatsi. Haeba o le sehlopha se sa fuweng moriana o fuputswang, re tla nka feela madi le ho etsa diteko tsa kutlo ditsebeng.

E le hore re utlwisise kamoo moriana o ka amang diphio tsa hao, re lakatsa ho hlahloba hape le tshebetso ya diphio. Diketelong tse 3 ho tse 9, ho tla hlokeha hape hore re nke 3 ml e nngwe ya madi, e le hore re ka lekanya tshebetso ya diphio tsa hao le ho etsa diphetoho tse nepahetseng tsa tekanyo ya moriana. Ka lebaka leo diketelong tseo re hlokang ho etsa teko ena, re tla hloka 3 ml e eketsehileng ya madi, e leng kahodimo feela ho halofo ya thispuni. Ka kakaretso, makgetlong a 3, re tla nka 9 ml ya madi, e leng ka tlase feela ho dithispuni tse pedi tse eketsehileng ho phaella ditekong tse ding tsa madi tse hlalositsweng ka hodimo mona. Re tla nka madi ana ka nako e tshwanang le ya teko ya madi bakeng sa kanamycin – e le hore ho se hlokehe hore o hlajwe ka ho eketsehileng ka nalete.

Ho nka madi ke karolo ya tlhokomelo ya hao e tlwaelehileng ya bongaka. Re hloka ho nka madi ka ho arohileng ho mekgwatshebetso e tlwaelehileng ya sepetlele. Sena se ka hlahisa kotsi e nyenyane ya makukuno. Re tla nka madi ka tsela e tshwanang le ha a nkuwa bakeng sa diteko tsa hao tse tlwaelehileng tsa madi. Ho nka madi ho ka etsa hore o akgehe, o ruruhe mothatswaneng wa madi, bohloko, ho tswa matetetso kapa ho tswa madi sebakeng se hlabilweng. Hape ho na le kgonahalo e

nyenyane ya ho ba le tshwaetso. Baoki ba nang le boiphihlelo kapa ditsebi tse hulang madi bakeng sa phuputso ba tla nka madi tlasa maemo a hlwekileng ho thusa ho etsa bonnete ba hore sena se bolokehile.

Madi a hao a tla bolokwa ka ho sireletsehileng Sepetleleng sa Helen Joseph ho fihlela a romelwa laboratoring bakeng sa diteko. A tla romelwa kapele kamoo ho ka kgonehang. A ke ke a bolokwa ho feta beke e le nngwe. Madi a hao a tla romelwa laboratoring e Sefako Makgatho Health Sciences University. Hamorao, madi ao re a nkileng bakeng sa ho lekanya tshebetso ya diphio tsa hao a tla romelwa laboratoring e nngwe, e bitswang CLS. Tlhahisoleseding kaofela ya hao mabapi le diteko tsena le mabapi le bophelo ba hao bo botle ka kakaretso e tla bolokwa lekunutung faeleng le ho kengwa khabotong nakong ya phuputso le kamora phuputso. Tlhahisoleseding ya hao e ke ke ya buisanwa le motho ofe kapa ofe e mong ya sa ameheng phuputsong. Haeba sena se hlokeha, re tla kopa tumello ya hao pele sena se etswa.

Diteko tsa ho utlwa le diteko tsa madi di tla etswa letsatsing la 2 (hosasane), matsatsing 15, 28, 40, 54, 68 le 84. Diteko tsa madi di tla etswa hosasane (letsatsi 2), letsatsing le latelang (letsatsi 3), mme e tla ba letsatsing le tshwanang jwaloka diteko tsa ho utlwa - matsatsing 15, 28, 40, 54, 68 le 84.

Ketelong e nngwe le e nngwe eo o tlang bakeng sa diteko tsa ho utlwa le tsa madi (e seng matsatsing a dipakeng ha o tla feela bakeng sa diente tsa hao), ketelo ka nngwe e tla nka hoo e ka bang dihora tse 5 ho ya ho tse 6. Ke hobane ho hlokeha hore re lete hoo e ka bang dihora tse 4 ho ya ho tse 6 pakeng tsa diteko tse 2 tsa madi. Kahoo, ho tla ba molemo haeba o ka tla esale hoseng, e le hore o ka tloha motshehare wa mantsiboya.

NA MEKGWATSHEBETSO EFE KAPA EFE ENA YA PHUPUTSO E TLA HLAHISA MAKUKUNO KAPA DITSHITISO?

Ho nka madi ho ka baka makukuno hanyenyane. Re tla nka madi ka tsela e tshwanang le eo re nkang madi bakeng sa diteko tse ding tsa hao tsa madi. Ho nka madi ho ka etsa hore o akgehe, o ruruhe mothatswaneng wa madi, bohloko, ho tswa matetetso kapa ho tswa madi sebakeng seo re nkileng madi ho sona. Hape ho na le kgonahalo e nyenyane ya ho ba le tshwaetso. Ke feela baoki ba nang le boiphihlelo (kapa ditsebi tse hulang madi bakeng sa phuputso) ba tla nka madi a hao ho thusa ho o sireletsa mme ntho e nngwe le e nngwe e tla ba e hlwekileng ka dinako tsohle. Kakaretso ya 4 ml ya madi (ke hore, a ka tlase feela ho thispuni) a tla nkuwa ketelong ka nngwe ya phuputso (ntle le letsatsing la 2 le la 3 – feela 2ml tse tla nkuwa). Kakaretso ya 28 ml, hoo e ka bang dithispuni tse 5 le halofo tsa madi. Ka mora moo, madi a eketsehileng a 3 ml a tla nkuwa matsatsing 40, 68 le 84 –

kakaretso e eketsehileng ya 9 ml e leng madi a ka tlase ho dithispuni tse 2. Ka lebaka lena, kakaretso ya 37 ml e tla nkuwa dikgweding tse tharo – a lekana le hoo e ka bang dithispuni tse 7 le halofo.

Diteko tsa kutlo tse hlalositsweng mona ka hodimo di ke ke tsa etsa hore o ikutlwe o sa phutholoha; le ha ho le jwalo, ho ntsha dikonokono ho ka ba bohloko hanyenyane. Le ha ho le jwalo, ha ho hlokehe hore re ntshe dikonokono mothong e mong le e mong, mme ha se ka dinako tsohle ho leng bohloko. Le ha ho le jwalo, ho ntsha dikonokono ho nka feela metsotswana e mmalwa. Teko kaofela e tla nka hoo e ka bang metsotso e 30 ho isa ho e 40 ya hao bakeng sa teko ka nngwe. Ka dinako tsohle o tla kgona ho buisana le mooki diphetho tsa hao le ho botsa dipotso pele le ka mora diteko tsena. Haeba o na le dipotso tse eketsehileng, o ka iteanya le nna, ngaka e hlahlobang kutlo ditseng.

MELEMO

Molemo o ka bang teng ka ho nka karolo ha hao phuputsong ena o tla kgona ho utlwisisa boemo ba hao ba ho utlwa ka ho fumana dintlha tse eketsehileng, le kamano ya kamoo kanamycin e sebediswang ke mmele wa hao.

- Ho ka etsahala hore o se une molemo phuputsong ena.
- Ho nka karolo ha hao phuputsong ena ho tla thusa mabapi le ho hodisa tsebo ya bongaka e ka thusang bakudi ba bang bao, jwaloka wena, ba nang le DR-TB le ba leng kotsing ya ho lahlehelwa ke kutlo ditsebeng.

KALAFO E NNGWE

- Nakong ya hajwale, ha ho na kalafo e nngwe e fokotsang kapa ho thibela tahlehelo ya kutlo ditsebeng e bakwang ke moriana wa DR-TB. Le ha ho le jwalo, haeba o ka lahlehelwa ke kutlo ditsebeng, o tla romelwa tliliniking ya sebakeng sa lona e haufi le wena ho fumana thuso ya ho fumana disebediswa tse thusang ho utlwa.
- Ho beha leihlo moriana kanamycin mading a hao ha se mokgwatshebetso o tlwaelehileng, mme hona jwale ha ho na mokgwa o mong ntle le diteko tsa madi ho etsa sena nakong ya jwale.
- Lefapha la Tlhahlobo ya Bongaka ya Kutlo Ditsebeng sepetleleng sena le tla kgona ho o thusa haeba o le sebakeng sena. Ena ke karolo ya mekgwatshebetso e tlwaelehileng ya mmuso mabapi le tlhokomelo ya tahlehelo ya kutlo ditsebeng. Ha se ka dinako tsohle disebediswa tse thusang ho utlwa di sebetsang.
- Haeba o etsa qeto ya hore o se nke karolo phuputsong ena o ntse o tla fumana tlhokomelo e molemohadi e fumanehang hajwale tliliniking ena bakeng sa DR-TB ya hao.

MELEMO LE DIKOTSI TSA KALAFO E NNGWE E TLWAELEHILENG

- Ka hobane hona jwale ha ho na moriana o ka thusang ho thibela tahlehelo ya kutlo kapa ho e fokotsa, ha ho na kalafo e nngwe. Haeba moriana wa hao wa DR-TB o baka tahlehelo ya kutlo, mme e le ka ho feletseng, e ke ke ya lokiswa. Empa o tla kgona ho fumana sesebediswa se thusang kutlo ho phahamisa medumo kaofela ho o thusa. Disebediswa tse thusang kutlo le ha ho le jwalo ha se ka mehla di thusang tahlehelong ya kutlo, ka hobane ka dinako tse ding tahlehelo ya kutlo e mpe haholo hoo disebediswa tse thusang kutlo di hlolehang ho o thusa. Ha re fane ka disebediswa tse thusang ho utlwa – lefapha la bongaka la tlhahlobo ya kutlo ditsebeng la sepetlele le tla kgona ho o thusa ka tsona haeba o sebakeng seo, kapa re tla o romela tliliniking kapa sepetleleng se nepahetseng sebakeng sa lona.
- Melemo ya disebediswa tse thusang ho utlwa e ka fokola, le ha ho le jwalo di ka o thusa haeba o qala ho ba le tahlehelo ya kutlo ho tswa moriana wa hao wa DR-TB. Disebediswa tse thusang ho utlwa ha di na dikotsi dife kapa dife.

NA HO NA LE DITEMOSO DIFE KAPA DIFE KAPA DITHIBELO MABAPI LE HO NKA KAROLO HA KA PHUPUTSONG ENA?

- Haeba o na le lefu la tswekere o ke ke wa nka karolo phuputsong ena. Ka dinako tse ding lefu la tswekere le ka ama kutlo, mme re lakatsa ho kgona ho lekanya kutlo ya hao ditsebeng ntle le tshitiso ena e ka etsahalang.
- Haeba o le ka tlase ho dilemo tse 18, kapa o le ka hodimo ho dilemo tse 55, o ke ke wa nka karolo phuputsong. Phuputsong ena, re nka ditekanyo tsa batho ba pakeng tsa dilemo tse 18 le 55.
- Haeba o bile lekgoba la sethethefatsi sefe kapa sefe mme o na le nalane ya tshebediso e mpe ya dithethefatsi kapa jwala, o ke ke wa kgona ho nka karolo phuputsong ena haeba sena se ka sitisa ho boloka ha hao mekgwatshebetso ya teko. Bafuputsi ba amehang ba tla etsa qeto mabapi le sena.

DITOKELO TSA HAO JWALOKA MONKAKAROLO PHUPUTSONG ENA

Boithaopo

Ho nka karolo ha hao phuputsong ena ho etswa ka boithaopo ka ho feletseng mme o ka kgetha haeba o lakatsa ho nka karolo kapa tjhe. Hape o ka kgaotsa ho nka karolo ka nako efe kapa efe mme ha ho hlokehe hore o fane ka lebaka. Haeba o kgetha hore o se nke karolo, kapa o etsa qeto ya ho kgaotsa ho nka karolo nakong ya phuputso, o tla tswela pele o fumana tlhokomelo ya bongaka sepetleleng sena, mme e ke ke ya sitiswa.

Diphumano tse ntjha

Ke tla o neha tlhahisoleseding efe kapa efe e ntjha eo ke e fumanang nakong ya phuputso, e ka fetolang boithaopo ba hao ba ho tswela pele phuputsong.

Ho ikgula/ho tloswa

Ho ikgula ha hao kapa ho kgaotsa ho nka karolo phuputsong ho ke ke ha sitisa tlhokomelo efe kapa efe e nngwe ya hao ya bongaka. Ke na le tokelo ya ho o tlosa phuputsong haeba e le ntho e molemong wa hao. Haeba ngaka ya hao e fetola moriana wa hao bakeng sa DR-TB mme o ke ke wa sebedisa kanamycin, o ke ke wa kgona ho tswela pele phuputsong ena. Haeba o sa fane ka tlhahisoleseding e nepahetseng le ya nnete mabapi le nalane ya hao ya bongaka, kapa o sa latele melao ya phuputso, nka o tlosa phuputsong ena ka nako efe kapa efe.

TLHOKOMELO MAEMONG A TSHOHANYETSO LE HO ROBATSWA SEPETLELE

Haeba o hloka tlhokomelo ya tshohanyetso ka nako efe kapa efe nakong ya phuputso, ka kopo letsetsa Ngaka Mohammed Rassool mona 011 276-8813 kapa 027 83 415 8967 kapa Ngaka Rebecca Berhanu mona 011276 8968 kapa 072 717 9159.

DITOKISETSO TSA DITJHELETE

- Batshehetsi ba ditjhelete ba phuputso ena ba tla lefella diteko tsohle tsa phuputso.
- Wena kapa medical aid ya hao (haeba o na le yona) le ke ke la lefella moriana ofe kapa ofe wa phuputso kapa mekgwatshebetso ya phuputso, mme kaofela di tshehetswa ka ditjhelete ke mekgatlo ya diphuputso.
- Ha o etela sepetlele bakeng sa phuputso bekeng e nngwe le e nngwe ya bobedi (bakeng sa diteko tse kutlo le diteko tsa madi) o tla fuwa R150 bakeng sa ho palama. O ke ke wa leshwa bakeng sa ho nka karolo, empa feela bakeng sa ho palama le dijo tse bobebe. Haeba o ya tliliniking ya heno letsatsi le letsatsi, o tla fuwa tjhelete ya ho palama. O tla fuwa R50 bakeng sa ho ya tliliniking ya heno letsatsi le letsatsi. Sena se tla etswa feela ka dikgwedi tsa pele tse 3. Ka mora dikgwedi tsena tse 3, ha ho tjhelete ya ho palama eo o tla e fuwa.

KAMOHELO YA BOITSHWARO

- Prothokhole ya phuputso ena ya moriana e dumeletswe ke Yunivesithi ya Witwatersrand, **Human Research Ethics Committee (HREC)** mme tumello e ngotsweng e fanwe ke komiti ena.
- Phuputso e latela ditataiso tsa **Phatlalatso ya Helsinki** (e ileng ya ntjhafatswa ka lekgetlo la ho qetela ka: Mphalane 2013), e sebetsanang le dikgothaletso bakeng sa dingaka tse etsang phuputso

ya bongaka ho bankakarolo ba batho. Haeba o lakatsa ho fumana kopi ya ditataiso tsena, ka kopo mpolelle, mme ke tla o fumanela tsona.

- Phuputso ena e lefellwa ke mokgatlo wa phuputso (South African Medical Research Council). Ha ke na dithahasello dife kapa dife tsa ditjhelete kapa tsa ka mokgatlong ona mme ha ke susumetswe kapa ho etswa leeme ke tsona.

INSHORENSE

Dingaka kaofela tsa bongaka phuputsong ena di na le inshorense. Mofuputsi ya ka sehloohong le dingaka di sireleditswe ka inshorense ke MPS ho tsamaisa mekgwatshebetso ha feela:

- Ba boloka mekgwatshebetso ya prothokhole ya phuputso.
- Ba boloka melao ya Medicines Control Council le ya Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC).
- Ba tshwara le ho fana ka moriana wa phuputso ho latela prothokhole le dihlomathiso le ditokomane tse ding tse amanang le yona.
- Ho tloswa qosong ya molato ha ho a rerelwa mme ha ho nka sebaka sa inshorense ya motho bakeng sa ketso efe kapa efe e mpe.

Ka kopo lemoha hore haeba o na le pholisi ya inshorense ya bophelo o tshwanetse ho botsa haeba khamphani ya hao ya inshorense e hloka hore e tsebiswe mabapi le ho nka karolo ha hao phuputsong. Ho tswa tlhahisoleseding e nngwe, sena ha se a lokela ho ama pholisi efe kapa efe ya bophelo eo o e nkileng. Empa ho ntse ho le bohlokwa ho hlahloba hape sena hobane ka dinako tse ding dikhamphani di a fapana.

MOHLODI WA TLHAHISOLESEDING E EKETSEHILENG

Nakong ya phuputso, o tla hlokomelwa ke moifo wa Sepetlele sa Helen Joseph. Haeba ka nako efe kapa efe o nahana hore o na le dipotso tse eketsehileng tse amanang le phuputso, ka kopo iteanye le nna kapa mooki wa phuputso/mohokahanyi ya leng mosebetsing sepetlele.

Litho tsa phuputso tseo o ka iteanyang le tsona:

- ✓ Cara Hollander – 082 815 8878 (Ngaka e hlahlobang kutlo ditsebeng)
- ✓ Ngaka Karin Joubert – 011 717 4561 (Ngaka e hlahlobang kutlo ditsebeng)
- ✓ Moprofesara Natalie Schellack – 012 521 3286 (Rakhemisi)
- ✓ Ngaka Rebbeca Berhanu – 011 276 8968 (Ngaka)
- ✓ Ngaka Mohammed Rassool –011 276-8813 (Ngaka le Mofuputsi ya ka Sehloohong)

- Haeba o batla tlhahisoleseding efe kapa efe mabapi le **ditokelo tsa hao jwaloka monkakarolo phuputsong, kapa o na le ditletlebo mabapi le phuputso ena,** o ka iteanya le Moprofesara Cleaton-Jones, Modula-setulo wa Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC), e leng komiti e ikemetseng e thusang ho sireletsa ditokelo tsa bankakarolo phuputsong mona (011) 717 2301.
- Bakeng sa **tlhahisoleseding ya phuputso** o ka iteanya le mohokahanyi wa Phuputso – Cara Hollander ho tswa Yunivesithing ya Witwatersrand mona 082 815 8878.

LEKUNUTU

- Tlhahisoleseding kaofela eo re e bokellang nakong ya phuputso ena, e kenyeletsang direkoto tsa sepetlele, tlhahisoleseding mabapi le wena le tlhahisoleseding ya phuputso e tla bolokwa e le lekunutu le thata. Ke feela ditho tsa moifo wa phuputso, le dingaka tsa hao le baoki ba tla fihlella tlhahisoleseding ya hao. Tlhahisoleseding efe kapa efe e tla ngolwa dikgatisong tsa saense kapa ntho efe kapa efe e tla hatiswa e ke ke ya ngolwa lebitso la hao.
- Re tla kenya dikhoutu tse fapaneng tlhahisoleseding ya hao ya phuputso. Ka lebaka lena, ha ho hlahlojwa diphetho tsa hao, ho tla ba le khoutu feela. Lebitso la hao, nomoro ya hao ya boitsebahatso kapa dinoutu dife kapa dife tse ding tse ka o tsebahatsang di ke ke tsa kengwa ditokomaneng tsena, ho etsa bonnete ba hore ntho e nngwe le e nngwe e bolokwa e le lekunutu.
- Tlhahisoleseding ena e tla hlahlojwa ke baemedi ba dumeletsweng ba Yunivesithi ya Witwatersrand le Yunivesithi ya Sefako Makgatho Health Science hammoho le ditho tse tswang ho batshehetsi ba ditjhelete (Medical Research Council). Diodithara tsa Wits Health Consortium di ka sheba diphetho tse itseng ha di etsa tlhahlobo ya tsona ho etsa bonnete ba hore ntho e nngwe le e nngwe e entswe ho latela ditekanyetso tse loketseng. Le ha ho le jwalo, ha se motho e mong le e mong ya tla fihlella lebitso la hao – diphetho tsohle tsa hao di tla kengwa nomoro, kahoo ba ke ke ba tseba hore ke wena.
- Tlhahisoleseding hape e ka hlahlojwa ke National Health Research Ethics Committee (NHREC), Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC), Medicines Control Council (MCC) ya Afrika Borwa le/kapa Food and Medicine Administration (FDA) ya United States hammoho le ngaka ya hao. Ka lebaka lena, o nneha tumello ya ho lokolla direkoto tsa hao tsa bongaka ho di neha Medical Research Council, basebetsi ba bona kapa dienjente, ba boholong ba bophelo bo botle hara naha le dinaheng disele, Medicines Control Council (MCC) ya Afrika Borwa, National Health Research Ethics Committee (NHREC) le Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC).
- Direkoto tsena di tla sebediswa ke bona feela ho etsa mesebetsi ya bona e amanang le phuputso ena ya moriana.

- Tlhahisoleseding efe kapa efe e fumanwang e amanang le diphetho tsa diteko tsa hao kapa boemo ba bophelo ba hao bo botle ka lebaka la ho nka karolo ha hao phuputsong ena e tla bolokwa e le lekunutu le thata. O tla bolellwa mabapi le diphumano dife kapa dife tsa bohlokwa bophelong ba hao bo botle kapa ho tswela pele ha hao phuputsong ena empa tlhahisoleseding ena e ke ke ya fuwa motho ofe kapa ofe wa boraro hammoho le batho ba seng ba boletswe mona ka hodimo ntle le tumello ya hao e ngotsweng. Mokgelo feela tabeng ena e tla ba diketsahalong tsa mafu a tshwaetsang moo e leng boikarabelo ba molao ho tsebisa Lefapha la Bophelo bo Botle ka ona. Ketsahalong e jwalo, ke tla o bolella mabapi le sena le hore ke tla neha lekgotla la mmuso le dumeletsweng tlhahisoleseding ena.

KGETHO YA HO TSEBISA NGAKA YA HAO / NGAKA E KGETHEHILENG

Ka kopo mpolelle mona ka tlase, haeba o lakatsa hore ke tsebise ngaka ya hao kapa ngaka ya hao e kgethehileng hore o nka karolo phuputsong ena:

- **E**, ke lakatsa hore o bolelle ngaka ya ka / ngaka e kgethehileng mabapi le ho nka karolo ha ka phuputsong ena.
- **TJHE**, ha ke lakatse hore o bolelle ngaka ya ka / ngaka e kgethehileng mabapi le ho nka karolo ha ka phuputsong ena.
- **Ha ke na** ngaka ya ka / ngaka e kgethehileng

DIPOTSO TSA BANKAKAROLO

Na wena, jwaloka monkakarolo, o na le dipotso dife kapa dife?

E / TJHE

Haeba E – Ka kopo hlalosa.

TUMELLO E BONTSHANG KUTLWISISO BAKENG SA BONKAKAROLO PHUPUTSONG

Ke netefatsa hore ke ile ka hlahiswa leseding ke mooki wa phuputso, ... *(LEBITSO LE FELETSENG)* mabapi le sebopeho, tsamaiso, melemo le dikotsi tsa phuputso e nang le sehlooho "Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng tsa ditekanyo tsa ho utlwa ditsebeng" (NOMORO YA PROTHOKHOLE 1.5).

- Hape ke amohetse, ke badile le ho utlwisisa tlhahisoleseding e ngotsweng mona ka hodimo (Maqephe a Tlhahisoleseding ya Monkakarolo le Tumello e Bontshang Kutlwisiso mabapi le phuputso ena ya moriana.
- Ke a lemoha hore diphetho tsa phuputso, ho kenyeletswa le tlhahisoleseding ya ka mabapi le bong, dilemo, letsatsi la tswalo, ditlhaku tse qalang tsa mabitso a ka le tlhahlobo ya bongaka ntle le lebitso la ka e tla etswa tlaleho ya phuputso.
- Ke a lemoha hore ho hlokeha hore ke tle tliliniking ya Helen Joseph bakeng sa dikgwedi tsena tse 3, beke e nngwe le e nngwe.
- Ke a lemoha hore nka ka kgetha ho ya tliliniking ya sebaka sa rona kapa ya Helen JosephHelen Joseph letsatsi le letsatsi bakeng sa diente tsa ka mme ke dumela ho etsa jwalo letsatsi le letsatsi.
- Ka lebaka la ditlhokeho tsa phuputso, ke dumela hore tlhahisoleseding e bokellwang nakong ya phuputso ena e ka kengwa sistiming ya khomphutha ke bafuputsi ba amehang phuputsong ena, batshehetsi ba ditjhelete kapa lebitsong la bona.
- Ke dumela ho nka karolo diseteng tse 7 tsa diteko tsa kutlo dikgweding tse 3 tsa pele.
- Ke dumela ho nka karolo diseteng tse 8 tsa diteko tsa madi dikgweding tsena tse 3.
- Ke dumela ho fana ka 2 ml tsa madi ka makgetlo a 2 dikgweding tse 3 tsa pele.
- Ke dumela ho fana ka 4 ml tsa madi ka makgetlo a 6 nakong ya phuputso. Le 9 ml tse ding bakeng sa ho etsa ditekanyo tsa ditshebetso tsa diphio dikgweding tse 3 tsa pele.
- Ke a tseba hore nka ikgula phuputsong ka nako efe kapa efe.
- Mohatong ofe kapa ofe, ntle le tshwaro e se nang leeme, nka hula tumello ya ka le bonkakarolo phuputsong.
- Ke bile le nako e lekaneng ya ho botsa dipotso mme (ka bolokolohi) ke bolela hore ke malala-a-laotswe ho nka karolo phuputsong.
- Ke a lemoha hore haeba ngaka ya e fetola moriana wa ka hore e be ntho e nngwe ntle le kanamycin, ke tla tloswa phuputsong.

MONKAKAROLO

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno / Letshwao kapa Kgatiso ya Monwana o Motona	Letsatsi le Nako

MOFUPUTSI YA TLASANA PHUPUTSONG

Nna, ..., ke netefatsa hore monkakarolo ya ngotsweng mona ka hodimo o ile a hlahiswa leseding ka ho feletseng mabapi le sebopeho, tsamaiso le dikotsi tsa phuputso e boletsweng ka hodimo mona.

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

MOFETOLEDI / MOTHO E MONG YA HLALOSANG TUMELLO E BONTSHANG KUTLWISISO (MOFUPUTSI YA TLASANA PHUPUTSONG)

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

PAKI (Haeba e hlokeha)

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

Appendix F

Information Leaflets and Informed Consent Form for **South Rand Hospital**: English

Information Leaflets and Informed Consent Form for **South Rand Hospital**: Zulu

Information Leaflets and Informed Consent Form for **South Rand Hospital**: SeSotho

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa
Postnet Suite

INFORMED CONSENT VERSION NUMBER: 1.5

(South Rand Hospital)

STUDY TITLE: A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels

INSTITUTION: University of the Witwatersrand in collaboration with Sefako Makgatho Health Sciences University

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S): 082 815 8878 (Cara Hollander) and/or011 681 2184 (Dr. Shilubane and Dr. Damoyi at South Rand Hospital) and /or +27 11 276-8813 (Dr. Mohammed Rassool – Principal Investigator – Doctor at Helen Joseph – Wits Health Consortium)

STUDY COORDINATOR: Matshediso Mkhwanazi: speed dial: 50017/ 076 711 2874/ Matshidiso.Mkhwanazi@righttocare.org

INTRODUCTION

Good day, my name is Cara Hollander and I am an audiologist from the University of the Witwatersrand. I would like to ***invite*** you to think about joining a research study, called "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels". We have just done some tests to confirm that you fit the criteria to take part in this study.

1. Before agreeing to take part in this study, it is important that you read and understand the following explanations about the reason for the study, the study procedures, benefits, risks, uncomfortable aspects, and precautions as well your right to pull out from the study at any time.

2. This information booklet is to help you to decide if you would like to take part. You need to understand everything about the study before you agree to take part in this study.

3. If you have any questions, please ask me.

4. You should not agree to take part unless you are happy about all the parts involved.

5. You may not take part in another research study while you are taking part in this study (unless it is approved by me beforehand).

6. Please be open with me about your health history, since you may otherwise harm yourself by taking part in this study.

7. If you decide to take part in this study, you will be asked to sign this form to confirm that you understand the study. You will be given a copy to keep.

8. If you have a personal doctor outside of this hospital, please discuss with or tell him/her of your possible participation in this study. If you would like, I can also tell your personal doctor about this.

PURPOSE OF THE STUDY

You are in this hospital/clinic because you have Drug Resistant Tuberculosis (DR-TB). I would like you to think about taking part in the research to measure your hearing levels throughout your DR-TB treatment. You will be receiving medicine (injections) to treat your drug resistant tuberculosis called kanamycin and/or capreomycin together with a few other medications, so that you can get better from your TB, which is very important. You will not be receiving kanamycin and capreomycin together, but may get them at different stages. They are both injections. The medicine you will be receiving is very strong, and has a few risks and one of them is hearing loss. However, you need to take this medicine so that you can get healthy again. Many people who take the medication will lose some of their hearing; but, although this happens often, it does not happen always. It can be very hard to talk to family and friends with a hearing loss and working can also be difficult. Therefore, during this research, we want to measure your hearing 7 times in the first three months, so that we can understand exactly what happens to your hearing. Then, we would also like to do blood tests 8 times in the first 3 months, so that we can look how your medicine for your DR-TB is working in your body. We will not changing or adjusting your DR-TB medicine based on the blood tests, but it will allow us to understand how the medicine works differently in different people, so that we can hopefully try and prevent hearing loss in the future. Your assistance will help us treat other patients in the future with this illness and it will also allow us to monitor your hearing throughout, and look at a relationship between how the drug is used in your body with your hearing.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS

The study will take place at this hospital as well as at Helen Joseph Hospital. About 80 people will take part in this study. The participants will be between the ages of 18 and 55 years. You will need to

take your kanamycin or capreomycin (depending on what your doctor decides) for more months than you will be part of this study. We will be doing tests for three months for this study, which will be explained below. These tests are blood tests and hearing tests. In the first 3 months, you will be asked to visit me 9 times for tests during the study. For some of these visits, you will be in hospital, and so they can be done in your ward or a separate room in the hospital. However, when you are discharged, you will need to come back to this hospital to see me, or to the TB focal point at Helen Joseph Hospital. If you are in hospital for 2 months, then you will only need to come see me as an outpatient for one month. But it will depend how long you are in hospital for. Today will be counted as day 1. You will ALSO need to go to your local clinic closest to your home every day (Monday to Friday) to get your injection from a nurse so she can record the time and dosage you are receiving (you will need to do this even if you are not part of the study as this is the standard of care). You will therefore need to go to South Rand Hospital or Helen Joseph Hospital (whichever one you prefer) once every second week for the hearing and blood tests, and then the local clinic daily. We will give you R150 for your travelling expenses every time you need to come to the hospital for the hearing and blood tests. When you are an inpatient in the hospital, you will not be paid for your transport, until you get discharged, as you will not need money for your transport. Then, we will give you enough money for your transport to go to the clinic every day (from Monday to Friday) to get your injections. We will give you R50 for your transport Monday to Friday to get your injections at your local clinic for the study period. When you come to the clinic for your 'official' study visits, when you have the hearing and blood tests we will give you R150. You will not get extra transport money that you get daily for coming for your injections on the days that you get R150.

PROCEDURES

If you agree to take part in this study, you will be asked questions and then will need to undergo a few tests – which will be hearing tests and blood tests. These tests will need to be done in addition to your other tests/procedures that are not study related.

If you agree to take part in this study and consent, I will need to ask you some questions today and examine you. Then, tomorrow, you will need more blood tests and the first hearing tests.

You will need to go to your local clinic every day (from Monday to Friday – not on the weekends) to get your kanamycin/capreomycin injection when you are discharged. Then, every second week, you will need to have blood tests and hearing tests. These days will take longer than your daily visits.

Purpose of hearing tests

Our ears are wonderful organs because they can hear so many difference pitches. We can hear low pitches which are for example a lawn mower, or a bus, or even a tap dripping. These are different sounds, and have different loudness levels, but they all have low pitches. Then we can also hear high pitches, for example birds tweeting or alarm clocks ringing.

Speech sounds, words and sentences are all different pitches. Like for example, the /m/, /d/ and /b/ are lower pitches where-as the /f/, /s/ and /th/ are higher pitches. In order for us to understand each other, we need to be able to hear many different frequencies or pitches, as speech sounds have many different pitches.

As soon as we start to only hear low pitches, and not the high pitches, then we struggle to understand speech. So, for example, when someone is saying ‘head’, you may mishear, and hear ‘bed’. If someone says ‘fate’, you may hear ‘ate’. Therefore a hearing loss at even a few frequencies will make it difficult to understand friends, family and doctors.

Many different things can cause hearing loss. Sometime people can be born with a hearing loss, or it could be from loud noise, trauma and some medicines. DR-TB is a serious illness, and you need very strong medicine to recover and live. However, sometimes, these medicines can cause a hearing loss, which could make it difficult for you to hear and communicate.

As the strong medicine (kanamycin/capreomycin) is needed to live, you have to take it. BUT, this research is to try to understand the exact kind of hearing loss that is caused by the medicine which will better allow for treatment or prevention in the future. We need to measure how you hear all the different sounds and pitches when you come into hospital, and then every few weeks, to see if its staying the same, or getting worse.

Hearing test procedures

A hearing test is not painful, and there are a few parts, as follows:

- Otoscopy – Firstly, I will need to look in your ears with a light to see if there is any wax, or other things in your ears, as this can affect your results. This will take about 20 seconds.
- Cerumen management – if your ears are clogged with wax, I will take the wax out so it doesn't affect the other tests. I will put some oil in your ear to make the wax soft. Then I will use a machine to pull out the wax (suction). The suction will only take a few seconds. It may be slightly painful, but it is not always painful.
- Tympanometry – Then, I will place a machine in your ear. It is a soft nub and it will pump some air in your ear. It will not be sore, but will help us know if you have any infections deep inside your ear, and if there is any fluid. If there is fluid, it will affect your hearing, and the results of the hearing test. This will take about 2 minutes.
- Distortion Product Otoacoustic Emissions – We have tiny hair cells deep in our ears. The different hair cells are important to hear the different pitches. Therefore, and DPOAE machine measures how these hair cells are moving and working. We need to put a soft nub in your ear, and it will make different sounds. You need to keep still and quiet, and the machine will take the measurements of these hair cells. This will take about 5 to 10 minutes.
- Pure Tone Audiometry – we will put headphones on you. They will give off very soft sounds. The sounds will have different pitches. Some will be low, and some will be high. Whenever you hear a sound, you will need to press a button. This will take about 15 to 20 minutes.

Once this is done, we are able to put all the results together and understand exactly what you are hearing. If we do the test when you come into hospital, and then we do it again at certain intervals, we can see if your hearing is changing.

If you agree to this, you will need to do this 7 times in the first 3 months. It would be tomorrow, then every second week for the next 3 months.

After 3 months of the study, you will continue to have your hearing monitored by the audiologists at this hospital or the hospital or clinic in your region. Should you get a hearing loss, they will continue to help you with hearing aids and further management. I will refer you to them after the study.

Blood Sampling

We will need to take blood as well. We will need to take blood so that we can measure how the DR-TB treatment (kanamycin/capreomycin) is being used in your body. We hope this will help us understand why people get a hearing loss. Myself, or another nurse, doctor or phlebotomist will take blood from you so that we can do the necessary tests. We need to take 2mls of blood for each test. You will need to have at least 2 blood tests each time (except for the first 2 visits). Two mls is about 2 drops of blood or half a teaspoon. Therefore, we will need to take 4mls of blood each day we see you to measure the kanamycin (just under a teaspoon of blood). The first time will be a few hours after you get your injection for your DR-TB. Then, the second time will be the following day before you get your injection. And the other times, you will need to get your blood taken before your injection, and a few hours after your injection. Therefore, for each visit (besides for the second visit when you have blood tests), you will need to be at the clinic for at least 4.5 hours (unless you are an inpatient, and are in the hospital anyway). We will need to do this 8 times all together over 3 months (tomorrow will be the first time). So altogether, over the 3 months, we will take a total of 28mls of blood, which is about 5 and a half teaspoons. We will therefore just be taking the blood and doing the hearing tests.

Then, in order to understand how the medicine may be affecting your kidneys, we would like to measure kidney function as well. On6 out of the 9 visits, we will also need to take another 3 mls of blood, so we can measure your kidney function and make the correct dosage changes. Therefore on the visits that we will need to test this, we need an extra 3mls of blood, with is just over half a teaspoon. Altogether, over the 3 times, we will draw 18 mls or blood, which is just over 3 teaspoons addition to the other blood tests described above. We will draw this at the same time at the blood test for the kanamycin/capreomycin– so that there will not be an extra needle prick.

Taking blood is part of your normal medical care at this hospital. We will need to take blood separately to the regular hospital procedures. This may present a slight risk of discomfort. We will draw the blood in the same way as it is taken for your general blood tests. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Experienced nurses, doctors or phlebotomists will take the blood in clean conditions to help make sure that is will be safe.

Your blood will be kept safely for no more than a day at South Rand Hospital, and then Helen Joseph Hospital until it is sent to the laboratory to be tested. It will be sent as soon as possible. It will not be kept for more than a week. Your blood will be sent to a laboratory at Sefako Makgatho Health

Sciences University. Then, the blood we take to measure your kidney function will be sent to another laboratory, called CLS. All the personal information about these tests and about your general health will be kept private in a file and then in a cupboard during after the research study. Personal information will not be discussed with any person not involved in the research study. If this is needed, we will ask for your permission before this is done.

The hearing tests and blood tests will be done on day 2 (tomorrow), days 15, 28, 40, 54, 68 and 84. The blood tests will take place tomorrow (day 2), the next day (day 3), and then on the same day as the hearing tests - on days 15, 28, 40, 54, 68 and 84.

At every visit that you come for the hearing and blood tests (not the days in between when you just come for your injections), each visit will take about 5 to 6 hours. This is because we need to wait about 4 to 6 hours between the 2 blood tests. So, it would be best if you came early in the morning, so you can leave by the afternoon.

WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

Taking blood may cause a small discomfort. We will take the blood in the same way as it is taken for your other blood tests. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding in the area that we take the blood from. There is also a slight chance of infection. Only experienced nurses (or phlebotomists or doctors) will take your blood to help protect you and everything will always be clean. A total of 4 mls of blood (i.e. just under a teaspoon) will be taken on each study visit (besides for day 2 and day 3 – only 2mls will be taken). This is a total of 28 mls, which is about 5 and a half teaspoons of blood. Then, an extra 3 mls will be drawn (except for the first two times) – and an extra total of 18 mls which just under over 3 teaspoons. Therefore, all together, 46 mls will be drawn over the three months – which is equivalent to just over 9 teaspoons.

The hearing tests as described above will not cause discomfort; however, taking out the wax may be slightly painful. We do not need to take out wax for every person though, and it is not always sore. Taking out the wax will only last a few seconds though. The rest of the test will take approximately 30 to 40 minutes of your time for each visit. You will always be able to discuss your results with the nurse and ask questions before or after these tests. If you have more questions, you can get in touch with myself, who is an audiologist.

BENEFITS

- The possible benefit from your participation in this study is, you will be able to understand your hearing status in more detail, and its relationship with how the kanamycin/capreomycinis being used in your body.
- You may not benefit from this study.
- Your participation in this study will help develop medical knowledge that may help other patients that, like you, have DR-TB and are at risk to develop a hearing loss.

ALTERNATIVE TREATMENT

- At the moment, there is no treatment to reduce or prevent the hearing loss caused by DR-TB medicine. Should you get a hearing loss; you will be referred to the local clinic nearest to you to assist you to receive a hearing aid.
- Monitoring the kanamycin/capreomycin in your blood is not a standard procedure, and there is no other way besides blood tests to do this at the moment.
- The Audiology Department at this hospital will be able to assist you if you are in this catchment area. This is part of general government procedures with hearing loss management.
- If you decide not to take part in this study you will still receive the best current care at this clinic for your DR-TB.

BENEFITS AND RISKS OF STANDARD ALTERNATIVE TREATMENT

- As there is currently no medicine that can help to prevent or lessen hearing loss, there is no other treatment. If your DR-TB medication causes a hearing loss, it is permanent, and cannot be fixed. But it will be possible to get a hearing aid to make all the sounds louder to help you. Hearing aids however cannot always help with hearing loss, as sometime the hearing loss is so bad, that the hearing aids cannot help. We will not be giving you the hearing aids – the hospitals audiology department will be able to assist you with that if you are in this catchment area, or we will refer you to the correct clinic or hospital that is in your catchment area.
- The benefits of the hearing aids can be limited, however may help you if you develop a hearing loss from your DR-TB medication. Hearing aids do not have any risks.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY

- If you have Diabetes Mellitus you may not take part in this study. Diabetes Mellitus can sometimes affect the hearing, and we want to be able to measure your hearing without this possibly interfering.

- If you are any younger than 18 years of age, or older than 55 years of age, you may not take part in the study. In this study, we are only measuring people between the ages of 18 and 55 years.
- If your doctor changes your medication (to anything other than kanamycin or capreomycin), you may not be able to continue participating in this study.
- If you have been addicted to any drug and have a history of drug or alcohol abuse, you cannot take part in the study if this could impact in your compliance with the test procedures. This will be decided at the discretion of the investigators involved.

RIGHTS AS A PARTICIPANT IN THIS STUDY

Voluntary

Your participation in this study is entirely voluntary and you can choose if you would like to take part or not. You can also stop taking part at any time and you do not need to give a reason. If you chose to not take part, or decide to stop taking part during the study, you will still get the medical care at this hospital, and it will not be affected.

New findings

I will provide you with any new information that I have during the study, which may change your willingness to continue on the study

Withdrawal

Your withdrawal or stopping participation in the study will not affect your other medical care. I have the right to withdraw you from the study if it is what is best for you. If your doctor changes your medicine for the DR-TB and you will not be taking kanamycin/capreomycin, then you will not be able to continue with this study. If you did not give correct and truthful information about your medical history, or did not follow the rules of the study, I may take you off the study at any time.

EMERGENCY CARE AND HOSPITALISATION

If you need emergency care at any time during the study, please call Dr. Damoyi or Dr. Shilubane on 011 681 2184 or Dr. Mohammed Rassool on 011 276-8813 (Helen Joseph Hospital – Principal Investigator) or 027 83 415 8967

FINANCIAL ARRANGEMENTS

- The funders of this study will provide payment for all study tests.
- Neither you nor your medical aid (if you have one) will need to pay for any study medication or study procedures, and they have been all funded by research organizations.
- When you visit the hospital for the study every second week (for hearing and blood tests) you will be provided with R150 for your transport (only once you are being treated as an outpatient). You will not be paid to take part, but only for your transport and refreshments. When you go to your local clinic daily or to this clinic daily, you will be compensated for your transport. You will be provided with R50 daily for your transport. This will only be for the first 3 months. After these 3 months, no money will be provided for your transport.

ETHICAL APPROVAL

- This clinical study protocol has been given to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been given by that committee.
- The study follows the guidelines of the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations for doctors in doing medical research with human participants. If you would like a copy of these principles, please let me know, and I will get them to you.
- This study is paid for by a research organisation (South African Medical Research Council). I do not have any financial or personal interests with this organization and I am not influenced or biased by them.

INSURANCE

All the medical doctors that are investigators in this study have insurance. The principal investigator and doctors are insured by MPS to conduct the procedures as long as:

- They obey the procedures of the study protocol.
- Their compliance with the rules of the Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication according to the protocol and amendments and other related documents.
- The indemnification is not intended to be and is not a substitute for any personal malpractice insurance.

Please note that if you have a life insurance policy you should find out if your insurance company needs to be notified about you taking part in the study. From other information, this should not affect any life insurance policy taken out. But it is still important to double check this as sometimes companies are different.

SOURCE OF ADDITIONAL INFORMATION

During the study, you will be cared for by the staff at South Rand Hospital. If at any time you feel that you have further study related questions, please contact me or the study nurse/coordinator on duty at the hospital.

Members (Investigators and Sub-Investigators) of the study who you can contact:

- Cara Hollander – 082 815 8878 (Audiologist)
- Dr. Karin Joubert – 011 717 4561 (Audiologist)
- Professor. Natalie Schellack – 012 521 3286 (Pharmacist)
- Dr. Shilubane – 011 681 2184
- Dr. Mohammed Rassool –011 276-8813 (Doctor and Principal Investigator)

If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee to help protect the rights of research participants at (011) 717 2301.

For **research information** you can contact the Study Planner– Cara Hollander from the University of the Witwatersrand on 082 815 8878.

CONFIDENTIALITY

- All information that we collect during this study, which includes hospital records, personal and research information will be kept strictly confidential. Only members of the research team, and your doctors and nurses will have access to your information. Any information that will be written in scientific journals or anything that is published will not have your name on.
- We will put different codes on your study information. Therefore, when reviewing your results, there will only be a code. Your name, identity number or any other identifying notes will not be on the documents, to ensure everything is confidential.
- This information will be reviewed by authorised representatives of the University of the Witwatersrand and Sefako Makgatho Health Sciences University as well and members from the funders (Medical Research Council). Auditors of the Wits Health Consortium may look at some of the results when they do their inspection to make sure everything is done with good standards. However, not everyone will have access to your name – all your results will have a number, so they will not know if it is you.
- The information might also be inspected by the National Health Research Ethics Committee (NHREC), University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC) and/or the United States Food and Medicine Administration (FDA) as well as your personal doctor. Therefore, you hereby authorize me to release your medical records to the Medical Research Council, its employees or agents, domestic and foreign regulatory health authorities, the South African Medicines Control Council (MCC), the National Health Research Ethics Committee (NHREC) and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- These records will be used by them only to carry out their duties relating to this clinical study.
- Any information uncovered regarding your test results or state of health as a result of your participation in this study will be strictly confidential. You will be told about any findings of importance to your health or continued participation in this study but this information will not be given to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, I will tell you about this and that I will be giving the information to be the authorised state agency.

PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION

Please tell me below, if you want me to notify your personal doctor or your specialist that you will be taking part in this study:

- **YES**, I want you to tell my personal doctor / specialist of my participation in this study.
- **NO**, I do not want you to tell my personal doctor / specialist of my participation in this study.
- **I do not have** a personal doctor / specialist

PARTICIPANT QUESTIONS

Do you, as the participant have any questions?

YES / NO

If YES – Please describe.

INFORMED CONSENT FOR PARTICIPATION IN THE STUDY

I hereby confirm that I have been informed by the study nurse/sub-investigator..... *(FULL NAME)* about the nature, conduct, benefits and risks of clinical study titled "A feasibility study investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels"

(PROTOCOL NUMBER 1.5)

- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) about this clinical study.
- I am aware that the results of the study, including personal details about my sex, age, date of birth, initials and diagnosis will be anonymously (my name will not be provided) processed into a study report.
- I am aware that I will need to come to the Helen Joseph clinic every second week for hearing and blood tests for 3 months.
- I am aware that I can choose to either go to my local clinic or the Helen Joseph clinic daily for my injections and I agree to do this daily.
- In view of the requirements of research, I agree that the data collected during this study can be put through a computerised system planned by the researchers involved in this study, the funders or on their behalf.
- I consent to participating in 7 sets of hearing tests in the first 3 months.
- I consent to participating in 8 sets of blood tests in these 3 months.
- I consent to give 2mls of blood 2 times in the first 3 months.
- I consent to giving 4mls of blood 6 times during the study. And another 18 mls to measure my kidney functions in the first 3 months.
- I do know that I can withdraw at any time.
- I may, at any stage, without unfairness, pull out my consent and participation in the study.
- I have had enough time to ask questions and (of my own free will) declare myself ready to participate in the study.
- I am aware that should my doctor change my medication to something other than kanamycin/capreomycin, I will be withdrawn from the study.

PARTICIPANT

_____

Printed Name Signature / Mark or Thumbprint Date and Time

STUDY SUB-INVESTIGATOR/ COORDINATOR

I, ..., herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

_____

Printed Name Signature Date and Time

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT (SUB-INVESTIGATOR)

_____

Printed Name Signature Date and Time

WITNESS (If applicable)

_____

Printed Name Signature Date and Time

INOMBOLO YOSHICILELO LWEMVUME ENIKEZWA EMVA KOKUTHOLA ULWAZI:

1.5

(Isibhedlela sase-South Rand)

ISIHLOKO SOCWANINGO: Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin isebenza kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa

ISIKHUNGO: I-University of the Witwatersrand ibambisene ne-Sefako Makgatho Health Sciences University

IZINOMBOLO ZOCINGO (ZEZINGCINGO) NGESIKHATHI SAMAHORA OKUSEBENZA NANGEMUVA KWAMAHORA OKUSEBENZA: 082 815 8878 (Cara Hollander) kanye/noma 011 681 2184 (Dkt. Shilubane no Dkt Damoyi esibhedlela sase-South Rand kanye /noma +27 11 276-8813 (Dkt. Mohammed Rassool – Umcwaningi Omkhulu – Udokotela wasesibhedlela sase Helen Joseph- Wits Health Consortium)

UMXHUMANISI WOCWANINGO: Matshediso Mkhwanazi: Inombolo yocingo esheshayo: 50017/ 076 711 2874 Matshidiso. Mkhwanazi@righttocare.org

Kulowo okunokwenzeka ukuba abambe iqhaza: *Leli fomu lemvume kungenzeka ukuthi liqukethe amagama ongawaqondisisi. Uyacelwa ukuba ubuze udokotela wocwaningo noma unesi wocwaningo noma umsebenzi wocwaningo ukuze akuchazele noma yimaphi amagama noma ulwazi ongaluqondisisi kahle. Ungakwazi ukuzigcinela* ***ikhophi elingasayiniwe lale mvume*** *ukuze ucabange ngalo noma uxoxe mayelana nalo nabomndeni wakho noma abangane bakho* ***ngaphambi kokuthatha isinqumo.***

ISINGENISO

Sawubona, igama lami nginguCara Hollander ngingudokotela wezinzwa zokuzwa wase-University of the Witwatersrand. Ngingathanda ukuba ucabange mayelana nokuhlanganyela kulolu cwaningo lophenyo, olwaziwa ngokuthi Ucwaningo lokuhlola ukuthi imithi i-kanamycin ne-capreomycin isebenza kanjani emzimbeni nemithelela yokusetshenziswa kwayo ezigulini ezine-DR-TB kanye nokuhlobana phakathi kwamazinga okuzwa. Sisandukwenza okunye ukuhlola okuqinisekisa ukuthi uyafaneleka ukubamba iqhaza kulolu cwaningo.

1. Ngaphambi kokuba uvume ukubamba iqhaza kulolu cwaningo, kubalulekile ukuthi ufunde lezi zincazelo ezilandelayo futhi uziqondisise ezimayelana nenhloso yalolu cwaningo,

izinqubo zocwaningo, izinsizakalo, ubungozi, izinto ezikwenza ungakhululeki, nezindlela zokuphepha kanye nelungelo lakho lokuhoxa kulolu cwaningo noma nini.

2. Leli bhukwana lolwazi lenzelwe ukukusiza ekuthatheni isinqumo sokuthi ungathanda yini ukubamba iqhaza. Kudingeka ukuba wazi yonke into mayelana nalolu cwaningo ngaphambi kokuvuma ukubamba iqhaza kulolu cwaningo.
3. Uma unemibuzo, ngicela ungibuze.
4. Akuphoqelekile ukuba ubambe iqhaza ngaphandle uma wenelisekile mayelana nazo zonke izingxenye ezibandakanyekayo.
5. Awuvunyelwe ukubamba iqhaza kolunye ucwaningo ngesikhathi usabambe iqhaza kulolu cwaningo (ngaphandle uma ngikunikile imvume ngaphambi kwalokho).
6. Ngicela ungangifihleli lutho mayelana nomlando wakho wezempilo, njengoba lokho kungenza ukuba uzilimaze ngokubamba iqhaza kulolu cwaningo.
7. Uma unquma ukubamba iqhaza kulolu cwaningo, uzocelwa ukuba usayine leli fomu ngenhloso yokuqinisekisa ukuthi uyaluqondisisa lolu cwaningo. Uzonikezwa ikhophi ukuba uzigcinele lona.
8. Uma unodokotela wakho ongasebenzi eHelen Joseph Hospital, ngicela uxoxe naye noma umtshele mayelana nokuthi kungenzeka ubambe iqhaza kulolu cwaningo. Uma uthanda, ngingamtshela mina udokotela wakho mayelana nalokhu.

INHLOSO YALOLU CWANINGO

Ukulesi sibhedlela noma ukulo mtholampilo ngoba unesifo sofuba esibizwa i-Drug Resistant Tuberculosis (i-DR-TB). Ngizothanda ukuba ucabange mayelana nokubamba kwakho iqhaza kulolu cwaningo lokukala amazinga akho okuzwa ngaso sonke isikhathi usalashelwa i-DR-TB yakho. Uzonikezwa umuthi (imijovo) wokwelapha isifo sakho sofuba esimelana nemithi obizwa nge-kanamycin kanye/noma ne-capreomycin neminye imithi embalwa, ukuze i-TB yakho ibe ngcono, okuyikho okubaluleke kakhulu. Ngeke uthole i-kanamycin ne-capreomycin kanye kanye, kodwa kungenzeka uyithole ezigabeni ezehlukene. Yomibili iyimijovo. Lo muthi ozonikezwa wona unamandla amakhulu futhi unobungozi obumbalwa, obunye balobu bungozi wukulahlekelwa wukuzwa. Noma kunjalo, kudingeka ukuba uwusebenzise lo muthi ukuze uphinde uphile kahle. Iningi labantu abasebenzisa lo muthi bazolahlekelwa wukuzwa; nakuba lokhu kuvame ukwenzeka, akwenzeki njalo. Kungaba nzima kakhulu ukukhuluma nomndeni kanye nabangane uma usungezwa ezindlebeni kanti nokusebenza kungaba nzima. Ngakho-ke, ngesikhathi kusaqhubeka lolu cwaningo, sifuna ukukala amazinga akho okuzwa izikhathi eziyisikhombisa ezinyangeni ezintathu zokuqala, ukuze siqonde kahle mayelana nokuthi yini eyenzeka ekuzweni kwakho. Emva kwalokho sizobe

sesikuhlola igazi izikhathi eziyisishiyagalombili ezinyangeni ezintathu zokuqala ukuze sibheke indlela umuthi wakho wokwelapha i-DR-TB osebenza ngayo emzimbeni wakho. Nizohlukaniswa ngamaqembu amabili. Mayelana neqembu elilodwa, kungenzeka sishintshe umithi wakho we-DR-TB yakho ukuze siqinisekise ukuthi umunceka kahle (awumunceki kakhulu ngokwedlulele noma kancane kakhulu). Nakuba lokhu kusahlolwa, sethemba ukuthi uma sishintsha umuthi wakho we-DR-TB, kungehlisa amathuba okulahlekelwa wukuzwa. Noma kunjalo, nakuba womabili amaqembu ezothathwa igazi, uzokwenziwa ushintsho eqenjini elilodwa kuphela, njengoba lokhu kuzovumela ukuba kuqhathaniswe amaqembu ashintshelwe umthamo nalelo qembu elingashintshelwanga umthamo ukuze kubonakale ukuthi yiliphi elilahlekelwe wukuzwa kancane. Nakuba kunjalo akubona bona bonke abantu abasebenzisa i-kanamycin abalahlekelwa wukuzwa. Uma ukulelo qembu lokulawula, ngeke siwushintshe umthamo wakho womuthi we-DR-TB yakho usizo lwakho luzosisiza ukwelapha ezinye iziguli ezinalesi sifo esikhathini esizayo futhi sizokwazi ukuqapha ukuzwa kwakho ngaso sonke isikhathi, kanye nokubheka ubudlelwano phakathi kwendlela lo muthi osebenzangayo emzimbeni wakho kanye nokuzwa kwakho.

Ubude besikhathi socwaningo kanye nenani lababambiqhaza

Lolu cwaningo luzokwenziwa kulesi sibhedlela kanye nasesibhedlela sase Helen Joseph.. Ngabantu abalinganiselwa kuma-80 abazobamba iqhaza kulolu cwaningo. Ababambiqhaza bazobe beneminyaka ephakathi kweyi-18 nengama-55 ubudala. Kuzodingeka ukuba usebenzise i-kanamycin noma icapreomycin (kuye ngokwesinqumo sikadokotela wakho) yakho ezinye izinyanga emva kokubamba iqhaza kulolu cwaningo. Sizokwenza ukuhlola izinyanga ezintathu zalolu cwaningo, okuzochazwa lapha ngezansi. Lokhu kuhlola wukuhlolwa kwegazi kanye nokuhlolwa kokuzwa. Ezinyangeni ezintathu zokuqala, uzocelwa ukuba ungivakashele izikhathi eziyi-9 ngenhloso yokuzohlolwa ngesikhathi kuqhubeka lolu cwaningo. Kokunye kwalokhu kuvakasha, uzobe usesibhedlela, ngakho-ke kungenzeka kwenziwe ewodini noma egumbini elehlukile esibhedlela. Kodwa-ke uma usudedeliwe, kuyodingeka ukuba ubuyele kulesi sibhedlela ukuze ubonane nami, noma uye esikhungweni esibhekana ne-TB esibhedlela sase Helen Joseph. Uma usesibhedlela izinyanga ezimbili, kuyodingeka ukuba uze ubonane nami njengesiguli esilashelwa ngaphandle, inyanga eyodwa. Kodwa kuyokuya ngokuthi uhlale esibhedlela isikhathi esingakanani. Usuku lwanamhlanje luzobalwa njengosuku loku-1. Kuzodingeka FUTHI ukuba uye emtholampilo oseduzane nekhaya lakho zonke izinsuku (uMsumbuluko kuya ngoLwesihlanu) ukuze uthole umjovo wakho kumhlengikazi ukuze arekhode isikhathi nesilinganiso ositholayo (kuzodingeka ukuba wenze lokhu ngisho ungeyona ingxenye yocwaningo njengoba lokhu kungukunakekelwa okwejwayelekile).Ngakho-ke kuzodingeka ukuba uye esibhedlela sase South Rand noma sase Helen Joseph (leso osincamelayo) kanye njalo emasontweni amabili ukuze wenze ukuhlolwa kokuzwa nokwegazi, bese uya emtholampilo wendawo zonke izinsuku.. Sizokukhokhela ama-R150 mayelana nezindleko zokugibela njalo nje uma kudingeka ukuba uze esibhedlela mayelana nokuzohlolelwa

ukuzwa negazi. Uma uyisiguli esilaliswe esibhedlela, ngeke ukhokhelelwe izindleko zokugibela kuze kube uyakhishwa esibhedlela njengoba ungeke ube nesidingo sokugibela. Bese sikunika imali eyanele yokugibela ukuze uye emtholampilo zonke izinsuku (ngoMsombuluko kuya ngoLwesihlanu) ukuze uthole imijovo yakho. Lokhu kuzokwenziwa izikhathi eziyi-9, njalo esontweni lesibili. Sizobe sesikunika imali eyanele yokugibela ukuza emtholampilo nsuku zonke (kusukela ngoMsombuluko kuya ngoLwesihlanu) ngenhloso yokuzothola imijovo yakho ye-kanamycin. Ngesikhathi uza emtholampilo mayelana nokuvakasha kwakho kocwaningo "okusemthethweni" uma uzohlolelwa igazi nokuzwa sizokunika ama-R150. Ngeke sikunike imali yokugibela ethe xaxa kunaleyo yansuku zonke uma uzele imijovo yakho ngalezo zinsuku onikezwa ngazo ama-R150.

IZINQUBO

Uma uvuma ukubamba iqhaza kulolu cwaningo, uzobuzwa imibuzo bese wenziwa ukuhlolwa okumbalwa – okuzobe kuwukuhlolelwa ukuzwa kanye nokuhlolwa kwegazi lakho. Lokhu kuhlolwa kuzokwenziwa ngaphezu kokunye ukuhlolwa/nezinqubo ezingahlobene nalolu cwaningo.

Uma uvuma ukubamba iqhaza kulolu cwaningo futhi unikeza imvume, kuzodingeka ukuba ngikubuze imibuzo embalwa namuhla bese ngikuhlola. Bese ubuya kusasa ukuze wenze okunye ukuhlolwa kwegazi nokuhlolwa kokuzwa kokuqala.

Kuzodingeka ukuba uye emtholampilo oseduze nawe nsuku zonke (kusukela ngoMsombuluko kuya kuLwesihlanu – hhayi ngezimpelasonto) ukuze uthole umjovo wakho we-kanamycin/we-capreomycin uma usukhishiwe esibhedlela. Bese kuthi njalo esontweni lesibili, kudingeke ukuba uhlolwe igazi uhlolelwe nokuzwa futhi. Lezo nsuku zizothatha isikhathi eside uma kuqhathaniswa nokuvakasha kwakho kwansuku zonke.

Inhloso yokuhlolelwa ukuzwa

Izindlebe zethu ziyizitho zomzimba ezimangalisayo ngoba ziyakwazi ukuzwa imisindo eminingi ehlukahlukene. Siyakwazi ukuzwa imisindo emincane njengomsindo owenziwa ngumshini wokugunda utshani, noma yibhasi, noma ngisho nokuconsa kwamanzi empompini. Le yimisindo ihlukahlukene, futhi inamazinga omsindo ahlukahlukene kodwa yonke le misindo iphansi. Futhi siyakwazi ukuzwa imisindo ephakeme, isibonelo izinyoni ezisho ngengila ephezulu noma ukukhala kwe-alamu yewashi.

Imisindo yenkulumo, amagama nemisho konke lokhu kuyimisindo ehlukahlukene. Isibonelo, u- /m/, u-/d/ no-/b/ kuyimisindo ephansi kodwa u-/f/, u-/s/ no-/th/ kuyimisindo ephezulu. Ukuze sizwane, kudingeka sikwazi ukuzwa imisindo eminingi ehlukahlukene, njengemisindo yenkulumo njengoba inemisindo eminingi ehlukahlukene.

Uma sesiqala sizwa imisindo ephansi yodwa, singasayizwa imisindo ephezulu, kusho ukuthi siyehluleka ukuzwa inkulumo. Ngakho, isibonelo, uma umuntu ethi 'head', awube usamuzwa kahle ucabange ukuthi uthi 'bed'. Uma umuntu ethi 'fate', ungezwa kuphela sengathi uthi 'ate'. Ngakho-ke ukulahlekelwa ukuzwa ngisho nasemisindweni embalwa kungenza ukuba ungakuqondi lokho okushiwo ngabangane bakho, umndeni kanye nabodokotela bakho.

Ukulahlekelwa wukuzwa kungadalwa yizinto eziningi ezihlukahlukene. Kwesinye isikhathi abantu kungenzeka bazalwe bengezwa kahle, noma kungenzeka ukungezwa kahle kudalwe ngumsindo ophezulu, wukwethuka ngokwedlulele kanye nemithi ethile. I-DR-TB yisifo esibi kakhulu futhi udinga umuthi onamandla amakhulu ukuze uphole uphinde uphile. Noma kunjalo, kwezinye izikhathi le mithi ingadala ukulahlekelwa wukuzwa, okungenza ukuba kube nzima kuwe ukuzwa nokuxhumana nabanye abantu.

Njengoba kudingeka umuthi onamandla kakhulu (i-kanamycin/i-capreomycin) ukuze uphile, kumele ukuba uwusebenzise. KODWA, lolu cwaningo luzama ukuqonda ngqo i uhlobo lokulahlekelwa wukuzwa oludalwa yilo muthi okuzokwenza ukukwelapha kangcono lokhu kulahlekelwa wukuzwa noma ukukuvikela esikhathini esiizayo.

Sidinga ukukala indlela ozwa ngayo imisindo ehlukahlukene ngesikhathi uza esibhedlela, bese kuthi emva kwalokho kube masonto onke ambalwa, ukuze sibone ukuthi kuhlala kunjalo noma kuya ngokuya kuba kubi.

<u>Izinqubo zokuhlola ukulahlekelwa wukuzwa</u>

Ukuhlolela ukuzwa akubuhlungu, futhi kunezingxenye ezimbalwa, ezimi kanje:

- I-otoscopy – Okokuqala, kuzodingeka ukuba ngibheke phakathi ezindlebeni zakho ukuze ngibone ukuthi akukho sigonogono yini, noma ezinye izinto ezindlebeni zakho, njengoba lokhu kungenzeka kube nomthelela emiphumelweni yakho. Lokhu kuzothatha cishe imizuzwana engama-20.
- Ukulawulwa kwesigonogono – Uma izindlebe zakho zivalekile ngenxa yesigonogono, ngizosikhipha ukuze singabi nomthelela kokunye ukuhlola. Ngizofaka amafutha endlebeni yakho ukuze isigonogono sakho sithambe. Ngizobe sengisebenzisa umshini ukukhipha isigonogono (ukusimunca). Ukumunca kuzothatha imizuzwana embalwa nje kuphela. Kungenzeka uzwe ubuhlungwana, kodwa akuvamile ukuba buhlungu.
- I-tympanometry (uhlobo lokuhlola okukala ukusebenza kwengxenye yendlebe ephakathi naphakathi) – ngizobe sengibeka umshini phakathi endlebeni yakho. Lo mshini othambile uzofuthela umoya endlebeni yakho. Ngeke kube buhlungu, kodwa kuzokwenza ukuba sazi ukuthi ingabe zikhona yini izifo ngaphakathi ekujuleni kwendlebe yakho, uma kukhona noma yiluphi uketshezi. Uma lukhona uketshezi, lizoba nomthelela ekuzweni kwakho kanye nasemiphumelweni yokuhlola. Lokhu kuzothatha cishe imizuzu emi-2.

- I-Distortion Product Otoacoustic Emissions – Sinamaseli ezinwedlana ekujuleni kwezindlebe zethu. Amaseli ezinwele ahlukahlukene abalulekile ekuzweni imisindo ehlukahlukene. Ngakho-ke umshini i-DPOAE ukala indlela lawa maseli ezinwele ahamba nasebenza ngayo. Sidinga ukufaka lo mshininyana othambile endlebeni yakho ukuze wenze imisindo ehlukahlukene. Kumele unganyakazi futhi uthule, lo mshni uzobe usuthatha izilinganiso zalawa maseli ezinwele. Lokhu kuzothatha cishe imizuzu emi-5 kuya kweyi-10.
- I-Pure Tone Audiometry – Sizokufaka ama-headphone. Azokhipha imisinjwana. Le misindo izoba namaphimbo ahlukahlukene. Amanye azoba phansi kanti amanye azoba phezulu. Lapho uzwa umsindo, kuzomele ucindezele inkinobho. Lokhu kuzothatha cishe imizuzu eyi-15 kuya kwengama-20.
- Uma lokhu sekwenziwe, sizobe sesikwazi ukuhlanganisa imiphumela bese siqonda kahle ukuthi yikuphi okwazi ukukuzwa. Uma sikuhlola ngesikhathi uza esibhedlela, bese sikuhlola futhi ngezikhathi ezithile, sizokwazi ukubona ukuthi ukuzwa kwakho kuyashintsha yini.

Uma ukuvuma lokhu, kuzodingeka ukuba ukwenze izikhathi eziyisi-7 ezinyangeni ezintathu zokuqala. Kungaba kusasa, bese kuba njalo esontweni lesibili ezinyangeni ezintathu ezilandelayo.

Emva kwezinyanga ezintathu zalolu cwaningo, odokotela abaphathelene nemizwa yokuzwa (audiologists) balesi sibhedlela noma esibhedlela noma emtholampilo wesifunda sakho bazoqhubeka nokuqapha ukuzwa kwakho. Uma kwenzeka ulahlekelwa wukuzwa, bazoqhubeka nokukusiza ngezinsizakuzwa kanye nokunye ukulawula ukuzwa kwakho. Ngizokudlulisela kubo emva kwalolu cwaningo.

<u>Amasampula egazi</u>

Sizodinga ukukuthatha negazi. Sizodinga ukukuthatha igazi ukuze sikwazi ukulinganisa indlela umuthi (i-kanamycin/i-capreomycin) osetshenziselwa ukwelapha i-DR-TB yakho ukuthi usetshenziswa kanjani emzimbeni wakho. Sethemba ukuthi lokhu kuzosisisza ukuba sikwazi ukuqonda ukuthi yingani abantu belahlekelwa wukuzwa. Mina noma omunye unesi noma i-phlebotomist sizokuthatha igazi ukuze senze ukuhlola okudingekayo. Sizodinga ukukuthatha ama-2 ml egazi mayelana nalokho nalokho kuhlola. Kuzodingeka ukuba okungenani sikuhlole igazi kabili ngaleso naleso sikhathi (ngaphandle kokuvakasha okubili kokuqala). Amamililitha amabili cishe alingane namaconsi amabili egazi noma uhhafu wethisipuni. Ngakho-ke, kuzodingeka ukuba sikuthathe ama-4 ml egazi ngalolo nangalolo suku esikubona ngalo ukuze sikale i-kanamycin (okuzoba yigazi elingaphansana kwethisipuni). Uma uqala ukuthathwa igazi kuzobe kungemva kwamahora ambalwa uthole umjovo wakho we-DR-TB. Bese sikuthatha igazi okwesibili osukwini olulandelayo ngaphambi kokuthola umjovo wakho. Kanti kwezinye izikhathi, kuzodingeka ukuba uthathwe igazi lakho ngaphambi kokuthola umjovo, <u>futhi</u> kumele kudlule amahora ambalwa emva kokuthola umjovo. Ngakho-ke mayelana nokuvakasha ngakunye (ngaphandle kokuvakasha kwesibili lapho uhlolelwa

igazi), kuzodingeka ukuba ube semtholampilo cishe amahora amane nesigamu (ngaphandle uma ulalisiwe uvele usesibhedlela). Kuzodingeka ukuba senze lokhu izikhathi eziyi-8 sezihlangene zonke ezinyangeni ezintathu (kusasa kuzobe kungokokuqala). Ngakho-ke sekukonke, ezinyangeni ezintathu, sizothatha inani elingama-28 ml legazi selilonke, elicishe libe ngamathisipuni amahlanu nesigamu.

Ukuze siqonde ukuthi umuthi unamthelela muni ezinsweni zakho, sidinga nokukala ukusebenza kwezinso zakho. Ekuvakasheni okuyisithupha kwalokhu okuyisishiyagalolunye, sizodinga ukukuthatha elinye igazi elingama-3 ml, ukuze sikale ukusebenza kwezinso zakho ukuze senze ushintsho olulungile lomthamo. Ngakho-ke ngaleso sikhathi sokuvakasha lapho kuzodingeka ukuba sihlole lokhu, sizodinga amanye ama-3ml angeziwe egazi, okungaba ngaphezudlwana nje kwethisipuni. Kumahlandla amathathu sizokuthatha igazi elingama-18 ml selilonke, elingaba ngaphezudlwana kwamathisipuni amathathu ngaphezu kokunye ukuhlolwa kwegazi osekuchaziwe ngenhla. Sizokuthatha leli gazi ngesikhathi esisodwa nesokuhlolelwa igazi mayelana ne-kanamycin/ne-capreomycin – ukuze ungahlatshwa kaningi ngenalidi.

Ukuthathwa kwegazi kuyingxenye yokunakekelwa kwakho okuvamile ngokwezempilo kulesi sibhedlela. Kuzodingeka ukuba sikuthathe igazi kodwa lokhu singakuhlanganisi nezinqubo ezivamile zasesibhedlela. Lokhu kungakuzizwa ubuhlungwana. Sizokuthatha igazi ngendlela efanayo naleyo esetshenziswa uma uthathwa igazi ngenhloso yokuhlolelwa kwakho igazi okuvamile. Ukuthathwa kwegazi kungakwenza uquleke, uvuvuke umthambo wegazi, uzwe ubuhlungu, uhuzuke noma wophe lapho kungene khona inalidi. Kukhona namathuba amancane okusuleleka ngesifo. Ongcweti bamanesi noma bama-phlebotomist bazokuthatha igazi endaweni ehlanzekile ukuze baqinisekise ukuthi kuphephile.

Igazi lakho lizogcinwa liphephile isikhathi esingevile osukwini esibhedlela sase South Rand bese ligcinwa esibhedlela sase Helen Joseph kuze kufike leso sikhathi selithunyelwa elabhorethri ukuze liyohlolwa. Lizothunyelwa ngaphandle kokuchitha isikhathi. Ngeke ligcinwe isikhathi esingaphezu kwesonto. Igazi lakho liyothunyelwa elabhorethri yase-Sefako Makgatho Health Sciences University. Bese kuthi lelo gazi esilithathela ukukala ukusebenza kwezinso zakho lona lizothunyelwa kwenye ilabhorethri, ebozwa i-CLS. Lonke ulwazi oluqondene nawe ngqo mayelana nalokhu kuhlola namayelana nezempilo yakho jikelele kuzogcinwa kuyimfihlo efayilini ezohlala ekhabetheni ngesikhathi kuqhubeka lolu cwaningo nangesikhathi seluphothuliwe. Ulwazi oluqondene nawe ngqo ngeke kuxoxwe ngalo nomunye umuntu ongabandakanyekile kulolu cwaningo lophenyo. Uma lokhu kudingeka, sizocela imvume yakho ngaphambi kokuba kwenziwe. Lokhu sikudingela ukuqinisekisa ukuthi lonke ulwazi lurekhodwe ngendlela elungile, ngenhloso yokuqinisekisa ukuthi

sihlaziya imiphumela ukuze sibone ukuthi lokhu kuqashwa komuthi wokwelapha (okungukushintsha imithamo yakho ye-kanamycin) kusebenzile yini.

Ukuhlolelwa ukuzwa kanye nokuhlolwa kwegazi kuzokwenziwa ngosuku lwesibili (kusasa), nangosuku lwe-15, 28, 40, 54, 68 kanye nolwama-84. Ukuhlolwa kwegazi kuzokwenziwa kusasa (ngosuku lwesi-2), ngosuku olulandelayo (usuku lwe-3), bese kwenziwa ngosuku olulodwa lokuhlolelwa kwakho ukuzwa – osukwini lwe-15, 28, 40, 54, 68 kanye nangosuku lwama-84.

Lokho nalokho kuvakasha ngenhloso yokuzohlolelwa ukuzwa kanye nokuzohlolwa igazi (hhayi lezo zinsuku eziphakathi oza ngazo uma uzojovwa), kuzothatha cishe amahora ama-5. Lokhu kudalwa wukuthi sidinga ukuba silinde amahora amane nesigamu phakathi kokuhlolwa igazi okwenziwa kabili. Ngakho kungabangcono ukuba usheshe ufike ekuseni ukuze ukwazi ukubuyela emuva ntambama.

KUNGENZEKA YINI UKUTHI LEZI ZINQUBO ZINGIZWISE UBUHLUNGWANA NOMA ZINGIPHAZAMISE?

Ukuthathwa kwegazi kungakuzwisa ubuhlungwana. Igazi sizolithatha ngendlela efanayo naleyo esetshenziswayo ngesikhathi uhlolwa igazi. Ukuthathwa kwegazi kungakwenza uquleke, uvuvuke umthambo wegazi, uzwe ubuhlungu, uhuzuke noma wophe kuleyo ndawo elikhishwe kuyo. Kukhona namathuba amancane okungenwa yisifo. Igazii lakho lizothathwa ngamanesi (noma ama-phlebotomists) angongcweti ukuze uvikeleke futhi konke kuzobe kuhlanzekile ngaso sonke isikhathi. Uzothathwa isamba segazi elingama-4 ml (elingaphansana kwethisipuni) ngalokho nalokho kuvakasha kocwaningo (ngaphandle kosuku lwesi-2 nolwesi-3). Lesi yisamba esingama-28 ml egazi, okuyigazi elingacishe libe ngamathisipuni amahlanu nesigamu egazi. Uzobe usuthathwa elinye igazi elengeziwe elingama-3 ml ngosuku lwama-40, 68 nolwama-84 – isamba esengeziwe esingama-18 ml okuyigazi elingaphansana kwamathisipuni amabili. Ngakho-ke, selilonke igazi ozothathwa lona ezinyangeni ezintathu lingama-46 ml – okuyigazi elilingana cishe namathisipuni ayisi-7 nesigamu.

Lokhu kuhlolelwa ukuzwa okuchaziwe lapha ngenhla ngeke kukuzwise ubuhlungu; noma kunjalo, ukukhishwa kwesigonogono kungaba buhlungu. Angeke kube nesidingo sokukhipha wonke umuntu isigonogono, futhi akuvamile ukuba buhlungu. Ukukhishwa isigonogono kuzothatha imizuzwana embalwa nje kuphela. Kanti ukuhlola sekukonke kuzothatha isikhathi sakho esicishe sibe yimizuzu engama-30 kuya kwengama-40 ngalokho nalokho kuhlolwa. Uzokwazi ngaso sonke isikhathi ukuxoxisana nonesi mayelana nemiphumela yakho nokuthi ubuze imibuzo ngaphambi nangemuva kwalokhu kuhlola. Uma uneminye imibuzo, ungathintana nami, i-audiologist.

IZINZUZO

- Inzuzo ongayithola ngokubamba kwakho iqhaza kulolu cwaningo ukuthi uzokwazi ukuqonda isimo sokuzwa kwakho ngokugcwele nokuhlobana kwakho nokusebenza kwe-kanamycin/kwe-capreomycin emzimbeni wakho
- Kungenzeka ungazuzi lutho kulolu cwaningo.
- Ukubamba kwakho iqhaza kulolu cwaningo kuzosiza ekuthuthukiseni ulwazi kwezokwelapha olungasiza ezinye iziguli ezine-DR-TB njengawe futhi ezisengcupheni yokulahlekelwa wukuzwa.

ENYE INDLELA YOKWELASHWA

- Okwamanje, ayikho enye indlela yokwelapha ngenhloso yokwehlisa amathuba okulahlekelwa wukuzwa noma yokugwema ukulahlekelwa wukuzwa okudalwa ngumuthi we-DR-TB. Uma kwenzeka ulahlekelwa wukuzwa; uzodluliselwa emtholampilo wangakini ukuze ukusize uthole izinsizakuzwa.
- Ukuqapha i-kanamycin egazini lakho akuyona inqubo ejwayelekile, ayikho enye indlela yokwenza lokhu ngaphandle kokuhlola igazi okwamanje.
- I-Audiology Department kulesi sibhedlela izokwazi ukukusiza uma ukule ndawo ephakela lesi sibhedlela. Lokhu kuyingxenye yezinqubo zikahulumeni ezivamile mayelana nokuphathwa kokulahlekelwa wukuzwa. Uma unquma ukungalibambi iqhaza kulolu cwaningo, uzoqhubeka nokuthola ukunakekelwa okuhle okutholakayo njengamanje okuqondene ne-DR-TB yakho kulo mtholampilo.

IZINZUZO NOBUNGOZI BENYE INDLELA YOKWELASHWA ESEZINGENI

- Njengoba njengamanje ungekho umuthi ongasiza ekuvimbeleni noma ekwehliseni amathuba okulahlekelwa wukuzwa, awukho omunye umuthi. Uma umuthi we-DR-TB udala ukulahlekelwa wukuzwa, kuyaye kungalapheki futhi akukwazi ukulungiseka. Kodwa ungayithola insizakuzwa ezokwenyusa yonke imisindo ukuze usizakale. Noma kunjalo, kwesinye isikhathi izinsizakuzwa ziyaye zingasizi ngalutho, ngoba kuyenzeka ukuthi kwesinye isikhathi ukulahlekelwa wukuzwa kuyaye kube kubi kakhulu, okwenza ukuba izinsizakuzwa zingakwazi ukukusiza. Kwezinye izikhathi izinsizakuzwa angeke zikwazi ukukusiza mayelana nokulahlekelwa wukuzwa, njengoba kwesinye isikhathi ukulahlekelwa wukuzwa kuyaye kube kubi kakhulu ngendlela yokuthi izinsizakuzwa zingabe zisakwazi ukukusiza. Ngeke sikunikeze izinsizakuzwa – iminyango yezibhedlela ye-audiology ingakwazi ukukusiza ngalokho uma ukule ndawo ephakela lezi zibhedlela, noma singakudlulisela emtholampilo noma esibhedlela esilungile esikuleyo ndawo ephakela leso sibhedlela.

- Izinzuzo zezinsizakuzwa kungenzeka zibe nemikhawulo, kodwa-ke kungenzeka zikusize uma kwenzeka ulahlekelwa wukuzwa kwakho kusaqala ngenxa yokusebenzisa umuthi we-DR-TB. Izinsizakuzwa azinabo ubungozi.

INGABE ZIKHONA YINI IZEXWAYISO NOMA IMIBANDELA MAYELANA NOKUBAMBA KWAMI IQHAZA KULOLU CWANINGO

- Uma unesifo sikashukela i-Diabetes Mellitus awuvunyelwe ukubamba iqhaza kulolu cwaningo. I-Diabetes Mellitus kuyenzeka kwesinye isikhathi sibe nomthelela ekuzweni, kanti sifuna ukukala ukuzwa kwakho ngaphandle kokuthikamezeka.
- Uma uneminyaka yobudala engaphansi kweyi-18, noma uneminyaka yobudala engaphezulu kwengama-55, ngeke ukwazi ukubamba iqhaza kulolu cwaningo. Kulolu cwaningo sikala kuphela abantu abaphakathi kweminyaka yobudala eyi-18 nengama-55.
- Uma udokotela wakho ekushintshela kweminye imithi (okungeyona i-kanamycin noma i-capreomycin) ngeke ukwazi ukuqhubeka nokubamba iqhaza kulolu cwaningo.
- Uma udokotela wakho eshintsha imithi yakho, ngeke usakwazi ukuqhubeka nokubamba iqhaza kulolu cwaningo.
- Uma kade ungakwazi ukuphila ngaphandle kwanoma yisiphi isidakamizwa futhi unomlando wokusebenzisa budedengu izidakamizwa notshwala, ngeke ukwazi ukubamba iqhaza kulolu cwaningo uma lokhu kungaba nomthelela ekulandeleni kwakho imiyalelo yezinqubo zokuhlola. Isinqumo mayelana nalokhu sizothathwa abacwaningi ababandakanyekayo.

AMALUNGELO NJENGOMBAMBIQHAZA KULOLU CWANINGO

Ukuzithandela

Ukubamba kwakho iqhaza kulolu cwaningo kungukuzithandela kwakho futhi unokuzikhethela ukuthi uyafuna noma awufuni ukubamba iqhaza kulolu cwaningo. Futhi uyakwazi ukuyeka ukubamba iqhaza kulolu cwaningo noma nini ngaphandle kokunikeza isizathu. Uma unquma ukungalibambi iqhaza kulolu cwaningo, noma unquma ukuyeka ukubamba iqhaza ngesikhathi kusaqhubeka lolu cwaningo, uzoqhubeka nokuthola unakekelo lwezempilo kulesi sibhedlela, futhi ngeke lokhu kuthinteke.

Okusha okutholwayo

Ngizokunikeza noma yiluphi ulwazi olusha enginalo ngesikhathi kusaqhubeka lolu cwaningo, okungenzeka lukwenze ushintshe umqondo wakho wokufisa ukuqhubeka ukulolu cwaningo.

Ukuhoxa

Ukuhoxa kwakho noma ukuyeka ukubamba iqhaza kulolu cwaningo ngeke kuthinte ukunakekelwa kwakho ngokwezempilo. Nginelungelo lokukuhoxisa kulolu cwaningo uma lokho kuzosiza wena. Uma udokotela wakho eshintsha imithi yakho ye-DR-TB futhi ungasasebenzisi i-

kanamycin/i-capreomycin, ngeke usakwazi ukuqhubeka nokubamba iqhaza kulolu cwaningo. Uma unganikezanga ulwazi olulungile nolwethembekile mayelana nomlando wakho wezempilo, noma ungalandelanga imithetho yalolu cwaningo, ngizokukhipha kulolu cwaningo noma nini.

UKUNAKEKELWA NGAPHANSI KWEZIMO EZIPHUTHUMAYO KANYE NOKUNGENISWA ESIBHEDLELA

Uma udinga usizo oluphuthumayo noma nini ngesikhathi kuqhubeka lolu cwaningo, uyacelwa ukuba ushayele uDkt Damoyi noma uDkt Shilubane kule nombolo: 011 681 2184 noma uDkt Mohammed Rassool ucingo kule nombolo: 011 276-8813 noma kule nombolo: 027 83 415 8967 noma ushayele uDkt Rebecca Berhanu kule nombolo: 011276 8968 noma kule nombolo: 072 717 9159.

AMALUNGISELELO EZEZIMALI

- Abaxhasi balolu cwaningo bazokhokhela konke ukuhlola okuzokwenziwa kulolu cwaningo.
- Wena nabe-medical aid yakho (uma unayo) angeke kudingeke ukuba nikhokhele noma yimiphi imithi yalolu cwaningo noma izinqubo zalolu cwaningo, konke lokhu kuxhaswe yizinhlangano zalolu cwaningo.
- Ngesikhathi uvakashela esibhedlela ngokwalolu cwaningo njalo esontweni lesibili (ukuze uhlolelwe ukuzwa kanye nokuhlolwa igazi) uzonikezwa ama-R150 okugibela (kuphela uma usuyisiguli eselashelwa ngaphandle). Ngeke ukhokhelwe ngokubamba iqhaza, kodwa uzokhokhelwa kuphela imali yokugibela neyokudla okulula. Uma uza nsuku zonke ukuzothola umjovo wakho kanye noshintsho lomthamo okungenzeka lwenziwe, uzonikezwa imali eyanele yokugibela Uzonikezwa ama-R50 wokugibela nsukuzonke. Lokhu kuzokwenziwa kuphela ezinyangeni ezintathu zokuqala. Emva kwalezi zinyanga ezintathu, uzothola umjovo wakho emtholampilo oseduze nawe, kanti ayikho imali yokugibela ozonikezwa yona.

IMVUME YENKAMBISO ELUNGILE

- Iphrothokholi yalolu cwaningo lwezokwelapha isinikeziwe ku-University of the Witwatersrand, **Human Research Ethics Committee (HREC)** kantileli komidi isinikezele ngemvume ebhalwe phansi.
- Lolu cwaningo lulandela imihlahlandlela ye-**Declaration of Helsinki** (egcine ukubuyekezwa: ngo-Okthoba 2013), ebhekele izincomo mayelana nodokotela abenza ucwaningo lwezokwelapha olubandakanya ababambiqhaza okungabantu. Uma ufisa ukuthola ikhopho yale migomo, ngicela ungazise ukuze ngikutholele lona.

- Lolu cwaningo lukhokhelwe yinhlangano yocwaningo (i-South African Medical Research Council). Akukho nzuzo engiyibhekile yemali noma mina angeke ngizuze ngalutho kule nhlangano futhi ayikho ingcindezi engiyithola kule nhlangano noma angichemile nayo.

UMSHWALENSE

Bonke odokotela abangabacwaningi kulolu cwaningo banomshuwalense. Umcwaningi omkhulu nodokotela banomshuwalense we-MPS ukuba benze izinqubo uma nje:

- Behlonipha izinqubo zephrothokholi yocwaningo.
- Behambisana nemithetho yesigungu esilawula imithi neye-University of the Witwatersrand Research Ethic Committee.
- Bephatha imithi yocwaningo ngokwephrothokholi nokugguqulwa kwayo kanye nemibhalo ehlobene.
- Lokhu kuvikela akuhlosile futhi akuthathi indawo yomshuwalense yokungasebenzi komuntu ngendlela efanele
- Sicela uqaphele ukuthi uma une-policy yomshuwalense wempilo kufanele utthole noma inkampani yomshuwalense idinga ukwaziswa mayelana nokubamba kwakho iqhaza ocwaningweni. Ngokolunye ulwazi, lokhu akufanele kuphazamise noma iyiphi enye i-policy yomshuwalense wempilo onayo. Kodwa kubalulekile ukuthi ubhekisise ngoba kuyenzeka izinkampani zingafani.

UMTHOMBO WOKUTHOLA OLUNYE ULWAZI

Ngesikhathi kusaqhubeka lolu cwaningo, uzonakekelwa ngabasebenzi basesibhedlela sase South Rand.. Noma nini uma ufisa ukubuza eminye imibuzo ehlobene nalolu cwaningo, ngicela ungithinte noma uthinte unesi wocwaningo/umdidiyeli wocwaningo osemsebenzini ngalesi sikhathi esibhedlela.

Amalungu (abacwaningi nabacwaningi abancane) ocwaningo ongaxhumana nawo:

- ✓ UCara Hollander – 082 815 8878 (oyi-Audiologist)
- ✓ UDkt. Karin Joubert – 011 717 4561 (oyi-Audiologist)
- ✓ USolwazi. Natalie Schellack – 012 521 3286 (onguSokhemisi)
- ✓ Dr. Shilubane – 011 681 2184
- ✓ UDkt. Rebbeca Berhanu – 011 276 8968 (ongudokotela)
- ✓ UDkt. Mohammed Rassool –011 276-8813 (ongudokotela Nomphenyi Omkhulu)

- Uma ufuna noma yiluphi ulwazi oluthe xaxa mayelana **namalungelo akho njengombambiqahaza ocwaningweni, noma uma ufuna ukudlulisa ukukhalaza mayelana nalolu cwaningo lophenyo**, ungaxhumana noSlz Cleaton-Jones, uSihlalo we-University of the Witwatersrand, Human Research Ethics Committee (HREC), okuyikomidi elizimele elisiza ekuvikelweni kwamalungelo ababambiqhaza ocwaningweni kule nombolo: (011) 717 2301.
- Mayelana **nolwazi olumayelana nocwaningo,** ungashayela umdidiyeli Wocwaningo – uCara Hollander wase-University of the Witwatersrand kule nombolo: 082 815 8878.

UBUMFIHLO

- Lonke ulwazi esiluqoqa ngesikhathi kuqhubeka lolu cwaningo, olubandakanya amarekhodi asesibhedlela, ulwazi oluqondene nomuntu ngqo kanye nolwazi olumayelana nocwaningo luzogcinwa luyimfihlo. Ulwazi lwakho luzobonwa ngamalungu eqembu locwaningo kuphela, kanye nosokotela bakho kanye namanesi. Noma yiluphi ulwazi oluzobe lubhalwe kumajenali esayensi noma nanoma yikuphi okushicilelwayo ngeke kube negama lakho kukho.
- Sizofaka amakhodi ahlukahlukene olwazini lwakho locwaningo. Ngakho-ke uma imiphumela yakho ibuyekezwa, izobe inekhodi kuphela. Igama lakho, inombolo yakho kamazisi noma nanoma yimaphi amanye amanothi okungenzeka akuhlonze ngeke kufakwe kulawo mabhukwana, ukuze kuqinisekiswe ukuthi konke kuyimfihlo.
- Lolu lwazi luzobuyekezwa ngabaphathiswa abagunyaziwe be-University of the Witwatersrand kanye nabase-Sefako Makgatho Health Sciences University kanye namalungu avela kubaxhasi (i-Medical Research Council). Abacwaningimabhuku be-Wits Health Consortium bavunyelwe ukubheka eminye imiphumela ngesikhathi behlola ngenhloso yokuqinisekisa ukuthi konke kwenziwe ngokulandela amazinga amahle. Nakuba kunjalo, akusiyena wonke umuntu ozofinyelela egameni lakho – yonke imiphumela yakho izoba nenombolo, okuzokwenza ukuba bangazi ukuthi nguwe.
- Kungenzeka futhi ukuthi ulwazi luhlolwe ngabe-National Health Research Ethics Committee (NHREC), yi-University of the Witwatersrand, Human Research Ethics Committee (HREC), yi-South African Medicines Control Council (MCC) kanye/noma yi-United States Food and Medicine Administration (FDA) kanye nodokotela wakho. Ngakho-ke lapha uyangigunyaza ukuthi ngikhulule amarekhodi akho ezokwelapha ngiwanike i-Medical Research Council, abasebenzi bayo noma ama-ejenti ayo, abasemagunyeni kwezokulawulwa kwezempilo bakuleli lizwe nabakwamanye amazwe, i-South African Medicines Control Council) i-MCC), i-National Health Research Ethics Committee (NHREC) kanye ne-University of the Witwatersrand, Human Research Ethics Committee (HREC).
- Lawa marekhodi azosetshenziswa yibo kuphela ekwenzeni imisebenzi yabo ehlobene nalolu cwaningo lwezokwelapha.

- Noma yiluphi ulwazi oludaluliwe mayelana nemiphumela yokuhlolwa kwakho noma isimo sakho sempilo ngenxa yokubamba kwakho iqhaza kulolu cwaningo luzohlala luyimfihlo. Uzotshelwa mayelana nanoma yikuphi okutholakele okubalulekile mayelana nezempilo yakho noma okubalulekile mayelana nokuqhubeka kwakho ukubamba iqhaza kulolu cwaningo, kodwa lolu lwazi ngeke lunikezwe noma yimuphi omunye umuntu phezu kwalabo abashiwo lapha ngenhla ngaphandle kwemvume yakho ebhalwe phansi. Esimweni lapho lo mthetho ungeke usebenze khona yikulezo zimo ezimayelana nezifo ezithathelanayo lapho umthetho okhona udinga ukuba kwaziswe aboMnyango Wezempilo. Uma kuba nesimo esinjalo, ngiyokwazisa ngaso ngiphinde ngikwazise futhi ukuthi lolo lwazi ngizoludlulisela kwi-ejenti kahulumeni egunyaziwe.

UKUKHETHA UKUBA KWAZISWE UDOKOTELA WAKHO/UNGOTI WAKHO

Ngicela ungitshele lapha ngezansi uma ufuna ukuba ngazise udokotela wakho noma isipeshalisti sakho mayelana nokuthi uzobamba iqhaza kulolu cwaningo:

- **YEBO**, ngifuna wena utshele udokotela wami noma isipeshalisti sami ngokubamba iqhaza kulolu cwaningo.
- **CHA**, angifuni ukuthi wena utshele udokotela wami noma isipeshalisti sami ngokubamba iqhaza kulolu cwaningo.
- **Anginaye** udokotela/isipeshalisti okungesami

IMIBUZO YOMBAMBIQHAZA

Ingabe unayo imibuzo njengombambiqhaza?

YEBO / CHA

Uma impendulo yakho kunguYEBO – Sicela uchaze.

IMVUME ETHATHWA EMVA KOKUNIKEZWA ULWAZI MAYELANA NOKUBAMBA IQHAZA KULOLU CWANINGO

Ngiyaqinisekisa lapha ukuthi unesi wocwaningo, ... (*IGAMA NGOKUGCWELE)* unginikezile ulwazi mayelana nesimo, ukuziphatha, izinsizakalo nobungozi obumayelana nalolu cwaningo lwezokwelapha olusihloko esithi "Ucwaningo oluhlola into ethembekayo ukuthi ingenzeka oluphenya mayelana nendlela i-kanamycin emunceka ngayo ezigulini ezine-DR-TB kanye nobudlelwane phakathi kwemithi yokwelapha eqashelwe namazinga okuzwa" (INOMBOLO YEPHROTHOKHOLI 1.5).

- Futhi ngilutholile lolu lwazi olubhalwe lapha ngenhla, ngalufunda ngaluqonda (Ibhukwana Lolwazi Lombambiqhaza kanye Nemvume Enikezwa Emva Kokunikezelwa Kolwazi) mayelana nalolu cwaningo lwezokwelapha.
- Ngiyazi ukuthi imiphumela yalolu cwaningo, okubandakanya imininingwane eqondene nomuntu ngqo emayelana nobulili bami, iminyaka yobudala, usuku lwami lokuzalwa, iziqalomagama kanye nokuhlonzwa kwesifo esithile kuzofakwa embikweni walolu cwaningo ngaphandle kokwaziswa ukuthi ngekabani (igama lami ngeke lidalulwe).
- Ngiyazi ukuthi kumele ngize emtholampilo wase Helen Joseph njalo esontweni lesibili enyangeni ukuze ngenze ukuhlolwa kokuzwa nokwegazi izinyanga ezintathu.
- Ngiyazi ukuthi ngingakhetha ukuya emtholampilo wendawo engihlala kuyo noma emtholampilo waseHelen Joseph nsukuzonke ukuze ngijove, futhi ngiyavuma ukwenza lokhu nsukuzonke.Ngokubhekelela izidingo zalolu cwaningo, ngiyavuma ukuthi imininingwane eqoqwe ngesikhathi kuqhubeka lolu cwaningo ifakwe ohlelweni lwekhompyutha oluhlelwe ngabacwaningi ababandakanyeka kulolu cwaningo, abaxhasi noma egameni labo.
- Ngiyavuma ukubamba iqhaza emasethini ayisi-7 okuhlolelwa ukuzwa ezinyangeni ezintathu zokuqala.
- Ngiyavuma ukubamba iqhaza emasethini ayisishiyagalombili okuhlolwa igazi kulezi zinyanga ezintathu.
- Ngiyavuma ukunikezela ngegazi elingama-2ml amahlandla amabili ezinyangeni ezintathu zokuqala.
- Ngiyavuma ukunikezela ngegazi elingama-4 ml amahlandla ayisithupha ngesikhathi kuqhubeka lolu cwaningo. Kanye nelinye elingama-18 ml ukuze kukalwe ukusebenza kwezinso zami i ezinyangeni ezintathu zokuqala.
- Ngiyazi ukuthi ngiyakwazi ukuhoxa noma nini.

- Ngingakwazi, kunoma yisiphi isigaba, ngaphandle kokuphathwa ngendlela engafanele, ukuhoxisa imvume yami kanye nokubamba kwami iqhaza ocwaningweni.
- Ngibe nesikhathi esanele sokubuza imibuzo futhi ngiyazisholo mina (ngokuzithandela) ukuthi ngikulungele ukubamba iqhaza kulolu cwaningo.
- Ngiyazi ukuthi uma kwenzeka udokotela wami eshintsha imithi yami enginika eminye ngaphandle kwe-kanamycin/capreomycin, ngizohoxiswa kulolu cwaningo.

UMBAMBIQHAZA

Igama elibhaliwe	Isignisha/Uphawu noma umaka wesithupha	Usuku Nesikhathi

UMCWANINGI OMNCANE/UMXHUMANISI

Mina, ..., ngiyaqinisekisa lapha ukuthi lo mbambiqhaza ongenhla unikeziwe ulwazi olugcwele mayelana nesimo, ukuziphatha nobungozi mayelana nalolu cwaningo olungenhla.

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

UMHUMUSHI / OMUNYE UMUNTU OCHAZA IMVUME EMVA KOKUNIKEZELWA KOLWAZI (UMCWANINGI OMNCANE)

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

UFAKAZI (uma ekhona)

Igama elibhaliwe	Isignisha	Usuku Nesikhathi

NOMORO YA VERSION YA TUMELLO E BONTSHANG KUTLWISISO:1.5

(Sepetlele sa South Rand)

SEHLOOHO SA PHUPUTSO: Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng tsa ditekanyo tsa ho utlwa ditsebeng

INSTITJHUSHENE: Yunivesithi ya Witwatersrand tshebedisanong le Yunivesithi ya Sefako Makgatho Health Sciences

(LI)NOMORO TSA MOHALA TSA LIHORA TSA MOTSHEHARE LE KA MORA TSHEBETSO: 082 815 8878 (Cara Hollander) le/kapa 011 681 2184 (Ngaka Shilubane le Ngaka Damoyi mona South Rand Hospita le/kapa +27 11 276-8813 (Ngaka Mohammed Rassool – Mofuputsi ya ka Sehloohong – Ngaka mona Helen Joseph – Wits Health Consortium)

MOHOKAHANYI EA PHUPUTSO: Matshediso Mkhwanazi: speed dial: 076 711 2874/ Matshidiso.Mkhwanazi@righttocare.org

Motho eo e ka bang Monkakarolo: *Foromo ena ya tumello e ka ba le mantswe ao o sa a utlwisiseng. Ka kopo kopa ngaka ya phuputso/mooki kapa moifo wa phuputso ho o hlalosetsa mantswe afe kapa afe ao o sa a utlwisiseng ka ho hlakileng. O ka boloka* ***kopi e sa saenwang yatumello ena*** *ya foromo ena ho nahana ka yona kapa ho buisana ka yona le lelapa kapa metswalle* ***pele o etsa qeto ya hao.***

SELELEKELA

Dumela, lebitso la ka ke Cara Hollander mme ke ngaka ya tlhahlobo ya kutlo ditsebeng ho tswa Yunivesithing ya Witwatersrand. Ke lakatsa ho o ***mema*** hore o nahane ka ho kena phuputsong, e bitswang "Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng ditekanyo tsa ho utlwa ditsebeng". Re entse diteko tse itseng ho netefatsa hore o a tshwaneleha bakeng sa ho nka karolo phuputsong ena.

1. Pele o dumela ho nka karolo phuputsong ena, ho bohlokwa hore o bale le ho utlwisisa ditlhaloso tse latelang mabapi le phuputso, mekgwatshebetso ya phuputso, melemo, dikotsi,

dikarolo tse bakang makukuno, le ditemoso hammoho le tokelo ya hao ya ho ikgula phuputsong ka nako efe kapa efe.

2. Bukana ena ya tlhahisoleseding e o thusa ho etsa qeto haeba o lakatsa ho nka karolo. Ho hlokeha hore o utlwisise ntho e nngwe le e nngwe mabapi le phuputso pele o dumela ho nka karolo phuputsong ena.
3. Haeba o na le dipotso dife kapa dife, ka kopo mpotse.
4. Ha o a tshwanela ho dumela ho nka karolo ntle le haeba o o thabela ho dikarolo tsohle tse amehang.
5. O ke ke wa nka karolo phuputsong e nngwe nakong eo o nkang karolo phuputsong ena (ntle le haeba ke dumella sena pele).
6. Ka kopo bua le nna o sa pate letho mabapi le nalane ya hao ya bophelo bo botle, hobane ho seng jwalo o ka ipeha kotsing haeba o nka karolo phuputsong ena.
7. Haeba o etsa qeto ya ho nka karolo phuputsong ena, o tla kotjwa hore o saene foromo ena ho netefatsa hore o utlwisisa phuputso. O tla fuwa kopi ya yona ho e boloka.
8. Haeba o na le ngaka ya hao kantle ho sepetlele sena, ka kopo buisana le yena kapa o mmolelle hore ho na le kgonahalo ya hore o nke karolo phuputsong ena. Haeba o lakatsa, nka bolella ngaka ya hao mabapi le sena.

SEPHEO SA PHUPUTSO

O sepetleng/tliliniking ena hobane o na le Lefuba le Lwantshang Moriana (DR-TB). Ke lakatsa hore o nahane ka ho nka karolo phuputso ho lekanya ditekanyo tsa kutlo ya hao nakong yohle ya karolo ya hao yaDR-TB. O tla amohela moriana (diente) ho alafa lefuba la hao le lwantshang moriana o bitswang kanamycin le/kapa capreomycinhammoho le meriana e meng, e le hore o ka ba betere lefung la hao la TB, e leng taba ya bohlokwa haholo. O ke ke wa fumantshwa kanamycin le capreomycin hammoho, empa o tla di fumana mekgahlelong e fapaneng. Ka bobedi ke diente.Moriana oo o tlang ho o fumana o matla haholo, mme o na le dikotsi tse mmalwa mme e nngwe ya tsona ke ho lahlehelwa ke ho utlwa ditsebeng. Le ha ho le jwalo, o tshwanetse ho sebedisa moriana ona e le hore o ikutlwe o le betere hape. Batho ba bangata ba sebedisang moriana ona ba tla lahlehelwa ke ho utlwa ditsebeng; empa, le hoja sena se etsahala kgafetsa, ha se etsahele kamehla. Ho ka ba thata haholo ho bua le lelapa le metswalle ha o lahlehetswe ke ho utlwa ditsebeng mme hape ho ka ba thata ho sebetsa. Ka lebaka lena, nakong ya phuputso ena, re lakatsa ho lekanya ho utlwa ditsebeng ka makgetlo a 7 dikgweding tsa pele tse tharo, e le hore re ka utlwisisa hantle hore na ho etsahalang ka ho utlwa ha hao ditsebeng. Mme re tla lakatsa ho etsa diteko tsa madi ka makgetlo a 8 dikgweding tsa pele tse 3, e le hore re ka sheba kamoo moriana wa hao bakeng sa DR-TB ya hao o

sebetsang kateng mmeleng wa hao. Le tla arolwa ka dihlopha tse 2. Sehlopha se seng, re ka fetola moriana wa hao wa DR-TB le hore o mongwa ka tekanyo e lekaneng (e seng o mongata haholo mme e seng o nyenyane haholo). Le hona ena e le phuputso, re tshepa hore ha re fetola moriana wa hao wa DR-TB, sena se ka fokotsa tahlehelo ya hao ya ho utlwa ditsebeng. Le ha ho le jwalo, dihlopha ka bobedi ke tla etswa diteko tsa madi, ke feela sehlopha se le seng se tla ba le diphetoho, sena se tla re lumella ho bapisa dihlopha ka diphetoho tsa tekanyo ya moriana sehlopheng se seng le sehlopha se se nang diphetoho tsa ditekanyo tsa moriana, mme tla ka kgona ho bona hore na ke sehlopha sefe se nang le tahlehelo e nyenyane ya ho utlwa ditsebeng. Le ha ho le jwalo, ha se batho kaofela ba sebedisang kanamycin ba lahlehelwang ke ho utlwa ditsebeng. Haeba o le sehlopheng sa fuputseng phetoho ya moriana, o ke ke wa fetola ditekanyo tsa hao tsa moriana wa DR-TB. Le ha ho le jwalo, thuso ya hao e tla re thusa ho alafa bakuli ba bang nakong e tlang ba nang le lefu lena mme hape ho tla re dumella ho beha leihlo ho utlwa ha hao ditsebeng nako ng yohle ya phuputso, le ho sheba kamano pakeng tsa kamoo moriana o sebediswang kateng ke mmele wa hao le kamoo o utlwang kateng ditsebeng.

NAKO YA PHUPUTSO LE PALO YA BANKAKAROLO

Phuputso e tla etsetswa sepetleng sena hammoho le Sepetleleng sa Helen Joseph. Batho ba ka bang 80 ba tla nka karolo phuputsong ena. Bankakarolo ba tla ba pakeng tsa dilemo tse 18 le 55 ka boholo. Ho tla hlokeha hore o sebedise kanamycin kapa capreomycin (ho itshetlehilwe ka qeto ya ngaka ya hao) ka dikgwedi tse fetang tseo o tla nka karolo ka tsona phuputsong ena. Re tla etsa diteko ka dikgwedi tse tharo bakeng sa phuputso ena, sena se tla hlaloswa mona ka tlase. Diteko tsena ke diteko tsa madi le diteko tsa ho utlwa ditsebeng. Dikgweding tsa pele tse 3, o tla kotjwa hore o nketele ka makgetlo a 9 bakeng sa diteko nakong ya phuputso. Bakeng sa diketelo tse ding, o tla ba sepetlele, mme ka hoo di ka etsetswa kamoreng ya bakudi sepetlele kapa kamoreng e ka thoko ya sepetlele. Le ha ho le jwalo, ha o ntshwa sepetlele, ho tla hlokeha hore o kgutlele sepetleleng sena ho tla mpona, kapa sebakeng sa TB mona Sepetleleng sa Helen Joseph. Haeba o le sepetlele ka dikgwedi tse 2, kahoo ho tla hlokeha hore o mpone feela jwaloka mokudi ya kantle ya sa robatsweng sepetlele bakeng sa kgwedi e le nngwe. Empa ho tla itshetleha ka hore na o robatswa sepetlele ka nako e telele hakae.Kajeno e tla balwa e le letsatsi 1. HAPE ho tla hlokeha hore o ye tliliniking e leng sebakeng sa lona e leng haufi haholo le ntlo ya hao letsatsi le leng le le leng (Mantaha ho isa ho Labohlano) ho fumana ente ho tswa ho mooki e le hore a ka ngola fatshe nako le tekanyo ya moriana eo o e fumantshwang (o tshwanetse ho etsa sena esita le haeba o se karolo ya phuputso ka hobane sena ke tlhokomelo e tlwaelehileng). Ka lebaka lena o tshwanetse ho ya Sepetleleng sa South Rand kapa Sepetleleng sa Helen Joseph (le ha e le efe eo o e kgethang) hammoho bekeng e nngwe le e nngwe ya bobedi bakeng sa diteko tsa kutlo ditsebeng le tsa madi, le ho ya tliliniking e leng sebakeng sa lona letsatsi le letsatsi. Re tla o neha R150 bakeng sa ditjeo tsa ho palama lekgetlo le leng le le leng haeba ho hlokeha hore o tle sepetlele bakeng sa diteko tsa ho utlwa le diteko tsa madi. Haeba o le mokudi

ya robaditsweng sepetlele, o ke ke wa leshwa bakeng sa ho palama, ho fihlela o ntshwa sepetlele, ka hobane o ke ke wa hloka tjhelete ya ho palama. Re tla o neha tjhelete e lekaneng bakeng sa ho palama ho tloha tliliniking letsatsi le leng le le leng (ho tloha ka Mantaha ho fihla ka Labohlano) ho fumana diente tsa hao. Re tla o neha R50 bakeng sa ho palama ka Mantaha ho fiha ka Labohlano ho fumana diente tsa hao tliliniking ya heno bakeng sa nako ya phuputso.Ha o tla tliliniking bakeng sa diketelo tsa 'semolao' tsa phuputso, le ha o etswa diteko tsa ho utlwa ditsebeng le diteko tsa madi re tla o neha R150. O ke ke wa fumana tjhelete e eketsehileng ya ho palama eo o e fumanang letsatsi le le letsatsi bakeng sa diente tsa hao matsatsing ao o fumanang R150.

MEKGWATSHEBETSO

Haeba o dumela ho nka karolo phuputsong ena, o tla botswa dipotso mme ho tla hlokeha hore o etse diteko tse mmalwa – e tla ba diteko tsa ho utlwa le diteko tsa madi. Ho tla hlokeha hore diteko tsena di etswe ho phaella ditekong tse ding tsa hao/mekgwatshebetso e sa amaneng le phuputso.

Haeba o dumela ho nka karolo phuputsong ena le ho fana ka tumello, ho tla hlokeha hore ke o botse dipotso tse itseng kajeno le ho o hlahloba. Jwale, hosasane ho tla hlokahala diteko tse eketsehileng tsa madi le diteko tsa pele tsa kutlo ditsebeng.

Ho tla hlokeha hore o tle letsatsi le leng le le leng (ho tloha ka Mantaha ho fihlela ka Labohlano - e seng mafelong a beke) ho fumana ente ya hao ya kanamycin/capreomycin. Hape re tla etsa diphetoho tekanyong ya hao ya moriana haeba ho hlokeha. Mme, bekeng e nngwe le e nngwe ya bobedi, ho tla hlokeha hore o etse diteko tsa madi le diteko tsa ho utlwa. Matsatsi ana a tla nka nako e telele ho feta diketelo tsa hao tsa kamehla.

Sepheo sa diteko tsa ho utlwa

Ditsebe tsa rona ke ditho tse hlollang ka hobane di ka kgona ho utlwa diphitjhi (pitch) tse mengata tse fapaneng. Re kgona ho utlwa phitjhi e tlase e jwaloka ya motjhini o kutang jwang, kapa bese, kapa esita le wa pompo e dutlang. Ena ke medumo e fapaneng, mme e na le ditekanyo tse fapaneng tsa modumo, empa kaofela e na le diphitjhi tse tlase. Hape re kgona ho utlwa phitjhi e phahameng, ka mohlala, ho lla ha dinonyana kapa ho lla ha alamo ya tshupanako.

Modumo wa puo, mantswe le dipolelo kaofela e na le diphitjhi tse fapaneng. Ka mohlala /m/, /d/ le /b/ ke medumo e tlase athe /f/, /s/ le /th/ ke diphitjhi tse phahameng. E le hore re utlwisisane, ho hlokeha hore re kgone ho utlwa di-frequency tse ngata tse fapaneng kapa diphitjhi, ka hobane medumo e jwalo ya puo e na le diphitjhi tse ngata tse fapaneng.

Ha re qala ho utlwa feela diphitjhi tse tlase, mme e seng diphitjhi tse phahameng, re qala ho ba le bothata ba ho utlwisisa puo. Ka mohlala, ha motho a re 'head', o ka utlwa hampe, mme o utlwe 'bed'. Haeba motho a re 'fate', o ka utlwa 'ate'. Ka lebaka lena tahlehelo ya ho utlwa esita le di-frequency tse mmalwa e tla etsa hore ho be thata ho utlwisisa metswalle, lelapa le dingaka.

Dintho tse ngata tse fapaneng di ka baka tahlehelo ya ho utlwa. Ka dinako tse ding batho ba belehwa ba na le tahlehelo ya ho utlwa, kapa e ka bakwa ke lerata le phahameng, trauma le meriana e meng. DR-TB ke lefu le totileng, mme o hloka moriana o matla haholo hore o hlaphohelwe le ho phela. Le ha ho le jwalo, ka dinako tse ding, meriana ena e ka baka tahlehelo ya kutlo, mme e ka etsa hore o be thata ho utlwa le ho buisana le ba bang.

Ka hobane moriana o matla (kanamycin/capreomycin) o hlokeha hore o phele, o tshwanetse ho o sebedisa. EMPA phuputso ena e leka ho utlwisisa hantle-ntle mofuta wa tahlehelo ya kutlo o bakwang ke moriana bakeng sa ho dumella kalafo e molemo haholwanyane kapa thibelo ya yona nakong e tlang. Ho hlokahala hore re lekanye kamoo o utlwang medumo kaofela e fapaneng le diphitjhi tsa modumo ha o tla sepetlele, mme ka dibeke tse ding le tse ding tse mmalwa, ho bona haeba boemo bo dula bo tshwana, kapa bo mpefala.

<u>Mekgwatshebetso ya teko ya kutlo ditsebeng</u>

Teko ya kutlo ditsebeng ha e bohloko, ho na le dikarolo tse mmalwa, jwaloka tse latelang:

- Otoscopy – Pele, ho hlokeha hore ke shebe hara ditsebe tsa hao ka kganya ho bona haeba ho na le dikonokono dife kapa dife ditsebeng, kapa dintho tse ding ditsebeng tsa hao, hobane sena se ka ama diphetho tsa hao. Sena se tla nka hoo e ka bang metsotswana e 20.
- Cerumen management – Haeba ditsebe tsa hao di thibane ka lebaka la dikonokono, ke tla di ntsha e le hore di se ame diteko tse ding tsa hao. Ke tla tshela oli e itseng tsebeng ya hao ho etsa hore dikonokono di be bonolo. E be ke sebedisa motjhini ho hula dikonokono. Kgulo ena e tla nka feela metsotswana e mmallwa. Ho ka utlwisisa bohloko hanyenyane, empa ha se ka dinako tsohle ho utlwisang bohloko.
- Tympanometry – E be ke kenya motjhini tsebeng ya hao. Ke nub e bonolo mme e tla pompela moya o itseng ka tsebeng ya hao. Ho ke ke ha o utlwisa bohloko, empa ho tla re thusa ho tseba haeba ho na le ditshwaetso dife kapa dife hara tsebe ya hao, le haeba ho na le mokedikedi ofe kapa ofe. Haeba ho na le mokedikedi, sena se tla ama ho utlwa ha hao, le ho ama diphetho tsa teko ya kutlo. Sena se tla nka hoo e ka bang metsotso e 2.
- Distortion Product Otoacoustic Emissions (DPOAE) – Re na le disele tse nyenyane tsa moriri hare-hare ditsebeng tsa rona. Disele tse fapaneng tsa moriri di bohlokwa bakeng sa ho utlwa diphitjhi tse fapaneng. Ka lebaka lena, motjhini wa DPOAE o lekanya

kamora disele tsena tsa moriri di sisinyehang kateng le ho sebetsa. Ho hlokahala hore re kenye nub e bonolo tsebeng ya hao, mme e tla etsa medumo e fapaneng. O tshwanetse ho dula o sa sisinyehe mme o kgutsitse, mme motjhini o tla nka ditekanyo tsa disele tsena tsa moriri. Sena se tla nka hoo e ka bang metsotso e 5 ho isa ho e 10.

- Pure Tone Audiometry – Re tla o rwesa di-headphone. Di tla ntsha medumo e bonolo haholo. Medumo e tla ba le diphitjhi tse fapaneng. Tse ding di tla ba tlase, mme tse ding di tla ba hodimo. Nako le nako ha o utlwa modumo, o tshwanetse ho tobetsa konopo. Sena se tla nka hoo e ka bang metsotso e 15 ho isa ho e 20.

Hang ha sena se entswe, re tla kgona ho bokella diphetho tsa hao hammoho le ho utlwisisa hantle seo o se utlwang ditsebeng. Haeba re etsa teko ena nakong eo o tlang sepetlele, mme re e etsa hape ka dinako tse itseng dipakeng, re tla kgona ho bona haeba kutlo ya hae e fetoha.

Haeba o dumela sena, ho tla hlokeha hore o etse sena ka makgetlo a 7 dikgweding tsa pele tse 3. E tla ba hosasane, le bekeng e nngwe le e nngwe ya bobedi bakeng sa dikgwedi tse 3 tse latelang.

Ka mora dikgwedi tse 3 tsa phuputso, kutlo ya hao e tla tswela pele e behilwe leihlo ke dingaka tse hlahlobang kutlo ditseng sepetleleng sena kapa tliliniking e leng sebakeng sa lona. Haeba o lahlehelwa ke kutlo, dingaka tsena di tla tswela pele ho o thusa ka disebediswa tse thusang ho utlwa le tlhokomelo e tswelang pele. Ke tla o romela ho tsona ka mora phuputso.

<u>Sampole ya Madi</u>

Ho hlokeha hore re nke madi. Ho hlokeha hore re nke madi e le hore re ka lekanya kamoo kalafo ya (kanamycin/capreomycin) e sebediswang kateng mmeleng wa hao. Re tshepa hore sena se tla re thusa ho utlwisisa hore na ke hobaneng ha batho ba lahlehelwa ke kutlo ditsebeng. Nna, kapa mooki e mong kapa setsebi se hulang madi bakeng sa phuputso re tla nka madi ho wena e le hore re ka etsa diteko tse hlokehang. Ho hlokeha hore re nke 2 ml tsa madi bakeng sa teko ka nngwe. Ho tla hlokeha hore bonyane o be le diteko tse 2 tsa madi lekgetlo ka leng (ntle le diketelong tse 2 tsa pele). 2 ml e ka ba marothodi a 2 a madi kapa halofo ya thispuni. Ka lebaka lena, re hloka 4ml tsa madi letsatsi ka leng ha re o bona e le hore re lekanye kanamycin (ka tlase ho thispuni e le nngwe ya madi). Lekgetlo la pele e tla ba dihora tse mmalwa ka mora ho fumana ente ya hao ya DR-TB. Ka mora moo, lekgetlong la bobedi le tla latelwa ke letsatsi pele o fumana ente ya hao. Mme makgetlong a mang, ho tla hlokeha hore ho nkuwe madi a hao pele o hlajwa ente, <u>le</u> dihora tse mmalwa ka mora ho hlajwa ka ente ya hao. Ka lebaka lena, bakeng sa ketelo ka nngwe (ntle le ketelong ya bobedi ha ho etswa diteko tsa madi), ho hlokeha hore o be tliliniking ka dihora tse 4.5 bonyane (ntle le haeba o le mokudi ya robaditsweng sepetlele, mme se o ntse o le sepetlele). Ho tla hlokeha hore re etse sena ka makgetlo a 8 kaofela

dikgweding tse 3 (hosasane e tla ba lekgetlo la pele). Ka hoo, dikgweding tse 3, re tla nka kakaretso ya 28 ml ya madi, hoo e ka bang dithispuni tse 5 le halofo. Haeba o le sehlopheng se fuputswang, re tla etsa diphetoho tekanyong ya moriana kanamycin enteng ya hao eo o e hlajwang letsatsi le letsatsi. Haeba o le sehlopha se sa fuweng moriana o fuputswang, re tla nka feela madi le ho etsa diteko tsa kutlo.

Jwale, e le hore re etse phetoho tekanyong ya moriana wa hao, ho hlokeha hore re utlwisise kamoo diphio tsa hao di sebetsang kateng, e le hore re ka etsa phetoho ntle le hore re ntshe kotsi diphio tsa hao. Haeba o le sehlopheng se sa fetoleng tekanyo ya moriana, re batla ho bona kamoo kanamycin e amang diphio tsa hao. Diketelong tse 6 ho tse 9, ho tla hlokeha hape hore re nke 3 ml e nngwe ya madi, e le hore re ka lekanya tshebetso ya diphio tsa hao le ho etsa diphetoho tse nepahetseng tsa tekanyo ya moriana. Ka lebaka leo diketelong tseo re hlokang ho etsa teko ena, re tla hloka 3ml e eketsehileng ya madi, e leng kahodimo feela ho halofo ya thispuni. Ka kakaretso, makgetlong a 3, re tla nka 18 ml ya madi, e leng ka hanyenyane kahodimo ho dithispuni tse 3 tse eketsehileng ho phaella ditekong tse ding tsa madi tse hlalositsweng ka hodimo mona. Re tla nka madi ana ka nako e tshwanang le ya teko ya madi bakeng sa kanamycin/capreomycin – e le hore ho se hlokehe hore o hlajwe ka ho eketsehileng ka nalete.

Ho nka madi ke karolo ya tlhokomelo ya hao e tlwaelehileng ya bongaka. Re hloka ho nka madi ka ho arohileng ho mekgwatshebetso e tlwaelehileng ya sepetlele. Sena se ka hlahisa kotsi e nyenyane ya makukuno. Re tla nka madi ka tsela e tshwanang le ha a nkuwa bakeng sa diteko tsa hao tse tlwaelehileng tsa madi. Ho nka madi ho ka etsa hore o akgehe, o ruruhe mothatswaneng wa madi, bohloko, ho tswa matetetso kapa ho tswa madi sebakeng se hlabilweng. Hape ho na le kgonahalo e nyenyane ya ho ba le tshwaetso. Baoki ba nang le boiphihlelo kapa ditsebi tse hulang madi bakeng sa phuputso ba tla nka madi tlasa maemo a hlwekileng ho thusa ho etsa bonnete ba hore sena se bolokehile.

Madi a hao a tla bolokwa ka ho sireletsehileng bakeng sa nako e sa fetseng letsatsi le le leng Sepetleleng sa South Rand, le ka mora moo Sepetleleng sa Helen Joseph ho fihlela a romelwa laboratoring bakeng sa diteko. A tla romelwa kapele kamoo ho ka kgonehang. A ke ke a bolokwa ho feta beke e le nngwe. Madi a hao a tla romelwa laboratoring e Yunivesithing ya Sefako Makgatho Health. Hamorao, madi ao re a nkileng bakeng sa ho lekanya tshebetso ya diphio tsa hao a tla romelwa laboratoring e nngwe, e bitswang CLS. Tlhahisoleseding kaofela ya hao mabapi le diteko tsena le mabapi le bophelo ba hao bo botle ka kakaretso e tla bolokwa lekunutung faeleng le ho kengwa khabotong nakong ya phuputso le kamora phuputso. Tlhahisoleseding ya hao e ke ke ya

buisanwa le motho ofe kapa ofe e mong ya sa ameheng phuputsong. Haeba sena se hlokeha, re tla kopa tumello ya hao pele sena se etswa.

Diteko tsa ho utlwa le diteko tsa madi di tla etswa letsatsing la 2 (hosasane), matsatsing 15, 28, 40, 54, 68 le 84. Diteko tsa madi di tla etswa hosasane (letsatsi 2), letsatsing le latelang (letsatsi 3), mme e tla ba letsatsing le tshwanang jwaloka diteko tsa ho utlwa - matsatsing 15, 28, 40, 54, 68 le 84.

Ketelong e nngwe le e nngwe eo o tlang bakeng sa diteko tsa ho utlwa le tsa madi (e seng matsatsing a dipakeng ha o tla feela bakeng sa diente tsa hao), ketelo ka nngwe e tla nka hoo e ka bang dihora tse 5. Ke hobane ho hlokeha hore re lete hoo e ka bang dihora tse 4.5 pakeng tsa diteko tse 2 tsa madi. Kahoo, ho tla ba molemo haeba o ka tla esale hoseng, e le hore o ka tloha motshehare wa mantsiboya.

NA MEKGWATSHEBETSO EFE KAPA EFE ENA YA PHUPUTSO E TLA HLAHISA MAKUKUNO KAPA DITSHITISO?

Ho nka madi ho ka baka makukuno hanyenyane. Re tla nka madi ka tsela e tshwanang le eo re nkang madi bakeng sa diteko tse ding tsa hao tsa madi. Ho nka madi ho ka etsa hore o akgehe, o ruruhe mothatswaneng wa madi, bohloko, ho tswa matetetso kapa ho tswa madi sebakeng seo re nkileng madi ho sona. Hape ho na le kgonahalo e nyenyane ya ho ba le tshwaetso. Ke feela baoki ba nang le boiphihlelo (kapa ditsebi tse hulang madi bakeng sa phuputso) ba tla nka madi a hao ho thusa ho o sireletsa mme ntho e nngwe le e nngwe e tla ba e hlwekileng ka dinako tsohle. Kakaretso ya 4 ml ya madi (ke hore, a ka tlase feela ho thispuni) a tla nkuwa ketelong ka nngwe ya phuputso (ntle le letsatsing la 2 le la 3 – feela 2ml tse tla nkuwa). Kakaretso ya 28 ml, hoo e ka bang dithispuni tse 5 le halofo tsa madi. Ka mora moo, madi a eketsehileng a 3 ml a tla nkuwa matsatsing 40, 68 le 84 – kakaretso e eketsehileng ya 18 ml e leng madi a ka kahodimo hanyenyane ho ho dithispuni tse 3. Ka lebaka lena, kakaretso ya 46 ml e tla nkuwa dikgweding tse tharo – a lekana le hoo e ka bang dithispuni tse kahodimo hanyenyane ho tse 9.

Diteko tsa kutlo tse hlalositsweng mona ka hodimo di ke ke tsa etsa hore o ikutlwe o sa phutholoha; le ha ho le jwalo, ho ntsha dikonokono ho ka ba bohloko hanyenyane. Le ha ho le jwalo, ha ho hlokehe hore re ntshe dikonokono mothong e mong le e mong, mme ha se ka dinako tsohle ho leng bohloko. Le ha ho le jwalo, ho ntsha dikonokono ho nka feela metsotswana e mmalwa. Teko kaofela e tla nka hoo e ka bang metsotso e 30 ho isa ho e 40 ya hao bakeng sa teko ka nngwe. Ka dinako tsohle o tla kgona ho buisana le mooki diphetho tsa hao le ho botsa dipotso pele le ka mora diteko tsena. Haeba o na le dipotso tse eketsehileng, o ka iteanya le nna, ngaka e hlahlobang kutlo ditseng.

MELEMO

- Molemo o ka bang teng ka ho nka karolo ha hao phuputsong ena o tla kgona ho utlwisisa feela boemo ba hao ba ho utlwa ka ho fumana dintlha tse eketsehileng, le kamano ya kamoo kanamycin/capreomycin e sebediswang ke mmele wa hao.
- Ho ka etsahala hore o se une molemo phuputsong ena.
- Ho nka karolo ha hao phuputsong ena ho tla thusa mabapi le ho hodisa tsebo ya bongaka e ka thusang bakudi ba bang bao, jwaloka wena, ba nang le DR-TB le ba leng kotsing ya ho lahlehelwa ke kutlo ditsebeng.

KALAFO E NNGWE

- Nakong ya hajwale, ha ho na kalafo e nngwe e fokotsang kapa ho thibela tahlehelo ya kutlo ditsebeng e bakwang ke moriana wa DR-TB. Le ha ho le jwalo, haeba o ka lahlehelwa ke kutlo ditsebeng, o tla romelwa tliliniking ya sebakeng sa lona e haufi le wena ho fumana thuso ya ho fumana disebediswa tse thusang ho utlwa.
- Ho beha leihlo moriana kanamycin/capreomycin mading a hao ha se mokgwatshebetso o tlwaelehileng, mme hona jwale ha ho na mokgwa o mong ntle le diteko tsa madi ho etsa sena nakong ya jwale.
- Lefapha la Tlhahlobo ya Bongaka ya Kutlo Ditsebeng sepetleleng sena le tla kgona ho o thusa haeba o le sebakeng sena. Ena ke karolo ya mekgwatshebetso e tlwaelehileng ya mmuso mabapi le tlhokomelo ya tahlehelo ya kutlo ditsebeng. Ha se ka dinako tsohle disebediswa tse thusang ho utlwa di sebetsang.
- Haeba o etsa qeto ya hore o se nke karolo phuputsong ena o ntse o tla fumana tlhokomelo e molemohadi e fumanehang hajwale tliliniking ena bakeng sa DR-TB ya hao.

MELEMO LE DIKOTSI TSA KALAFO E NNGWE E TLWAELEHILENG

- Ka hobane hona jwale ha ho na moriana o ka thusang ho thibela tahlehelo ya kutlo kapa ho e fokotsa, ha ho na kalafo e nngwe. Haeba moriana wa hao wa DR-TB o baka tahlehelo ya kutlo, mme e le ka ho feletseng, e ke ke ya lokiswa. Empa o tla kgona ho fumana sesebediswa se thusang kutlo ho phahamisa medumo kaofela ho o thusa. Disebediswa tse thusang kutlo le ha ho le jwalo ha se ka mehla di thusang tahlehelong ya kutlo, ka hobane ka dinako tse ding tahlehelo ya kutlo e mpe haholo hoo disebediswa tse thusang kutlo di hlolehang ho o thusa. Ha re fane ka disebediswa tse thusang ho utlwa – lefapha la bongaka la tlhahlobo ya kutlo ditsebeng la sepetlele le tla kgona ho o thusa ka tsona haeba o sebakeng seo, kapa re tla o romela tliliniking kapa sepetleleng se nepahetseng sebakeng sa lona.

- Melemo ya disebediswa tse thusang ho utlwa e ka fokola, le ha ho le jwalo di ka o thusa haeba o qala ho ba le tahlehelo ya kutlo ho tswa moriana wa hao wa DR-TB. Disebediswa tse thusang ho utlwa ha di na dikotsi dife kapa dife.

NA HO NA LE DITEMOSO DIFE KAPA DIFE KAPA DITHIBELO MABAPI LE HO NKA KAROLO HA KA PHUPUTSONG ENA?

- Haeba o na le lefu la tswekere o ke ke wa nka karolo phuputsong ena. Ka dinako tse ding lefu la tswekere le ka ama kutlo, mme re lakatsa ho kgona ho lekanya kutlo ya hao ditsebeng ntle le tshitiso ena e ka etsahalang.
- Haeba o le ka tlase ho dilemo tse 18, kapa o le ka hodimo ho dilemo tse 55, o ke ke wa nka karolo phuputsong. Phuputsong ena, re nka ditekanyo tsa batho ba pakeng tsa dilemo tse 18 le 55.
- Haeba ngaka ya hao e fetola moriana wa hao (bakeng sa moriana ofe kapa ofe o mong ntle le kanamycin kapa capreomycin), o ka nna wa se kgone ho tswela pele o nka karolo phuputsong ena.
- Haeba o bile lekgoba la sethethefatsi sefe kapa sefe mme o na le nalane ya tshebediso e mpe ya dithethefatsi kapa jwala, o ke ke wa kgona ho nka karolo phuputsong ena haeba sena se ka sitisa ho boloka ha hao mekgwatshebetso ya teko. Bafuputsi ba amehang ba tla etsa qeto mabapi le sena.

DITOKELO TSA HAO JWALOKA MONKAKAROLO PHUPUTSONG ENA

Boithaopo

Ho nka karolo ha hao phuputsong ena ho etswa ka boithaopo ka ho feletseng mme o ka kgetha haeba o lakatsa ho nka karolo kapa tjhe. Hape o ka kgaotsa ho nka karolo ka nako efe kapa efe mme ha ho hlokehe hore o fane ka lebaka. Haeba o kgetha hore o se nke karolo, kapa o etsa qeto ya ho kgaotsa ho nka karolo nakong ya phuputso, o tla tswela pele o fumana tlhokomelo ya bongaka sepetleleng sena, mme e ke ke ya sitiswa.

Diphumano tse ntjha

Ke tla o neha tlhahisoleseding efe kapa efe e ntjha eo ke e fumanang nakong ya phuputso, e ka fetolang boithaopo ba hao ba ho tswela pele phuputsong.

Ho ikgula/ho tloswa

Ho ikgula ha hao kapa ho kgaotsa ho nka karolo phuputsong ho ke ke ha sitisa tlhokomelo efe kapa efe e nngwe ya hao ya bongaka. Ke na le tokelo ya ho o tlosa phuputsong haeba e le ntho e molemong wa hao. Haeba ngaka ya hao e fetola moriana wa hao bakeng sa DR-TB mme o ke ke wa sebedisa kanamycin/capreomycin, o ke ke wa kgona ho tswela pele phuputsong ena. Haeba o sa fane ka tlhahisoleseding e nepahetseng le ya nnete mabapi le nalane ya hao ya bongaka, kapa o sa latele melao ya phuputso, nka o tlosa phuputsong ena ka nako efe kapa efe.

TLHOKOMELO MAEMONG A TSHOHANYETSO LE HO ROBATSWA SEPETLELE

Haeba o hloka tlhokomelo ya tshohanyetso ka nako efe kapa efe nakong ya phuputso, ka kopo letsetsa Ngaka Damoyi kapa Ngaka Shilubane mona 011 681 2184kapa Ngaka Mohammed Rassool mona 011 276-8813 (Sepetleleng sa Helen Joseph – Mofuputsi ya ka Sehloohong) kapa 027 83 415 8967.

DITOKISETSO TSA DITJHELETE

- Batshehetsi ba ditjhelete ba phuputso ena ba tla lefella diteko tsohle tsa phuputso.
- Wena kapa medical aid ya hao (haeba o na le yona) le ke ke la lefella moriana ofe kapa ofe wa phuputso kapa mekgwatshebetso ya phuputso, mme kaofela di tshehetswa ka ditjhelete ke mekgatlo ya diphuputso.

  Ha o etela sepetlele bakeng sa phuputso bekeng e nngwe le e nngwe ya bobedi (bakeng sa diteko tse kutlo le diteko tsa madi) o tla fuwa R150 bakeng sa ho palama (feela haeba o alashwa jwaloka mokudi ya kantle ho sepetlele). O ke ke wa leshwa bakeng sa ho nka karolo, empa feela bakeng sa ho palama le dijo tse bobebe. Ha o tla letsatsi le letsatsi bakeng sa feela ho hlajwa ente le diphetoho tse ka bang teng tsa tekanyo ya moriana, o tla fuwa tjhelete e lekaneng bakeng sa ho palama. O tla fuwa R50 letsatsi le letsatsi bakeng sa ho palama. Sena se tla etswa feela ka dikgwedi tsa pele tse 3. Ka mora dikgwedi tsena tse 3, mme ha ho tjhelete ya ho palama eo o tla e fuwa.

KAMOHELO YA BOITSHWARO

- Prothokhole ya phuputso ena ya moriana e dumeletswe ke Yunivesithi ya Witwatersrand, **Human Research Ethics Committee (HREC)** mme tumello e ngotsweng e fanwe ke komiti ena.
- Phuputso e latela ditataiso tsa **Phatlalatso ya Helsinki** (e ileng ya ntjhafatswa ka lekgetlo la ho qetela ka: Mphalane 2013), e sebetsanang le dikgothaletso bakeng sa dingaka tse etsang phuputso ya bongaka ho bankakarolo ba batho. Haeba o lakatsa ho fumana kopi ya ditataiso tsena, ka kopo mpolelle, mme ke tla o fumanela tsona.
- Phuputso ena e lefellwa ke mokgatlo wa phuputso (South African Medical Research Council). Ha ke na dithahasello dife kapa dife tsa ditjhelete kapa tsa ka mokgatlong ona mme ha ke susumetswe kapa ho etswa leeme ke tsona.

INSHORENSE

Dingaka kaofela tsa bongaka phuputsong ena di na le inshorense. Mofuputsi ya ka sehloohong le dingaka di sireleditswe ka inshorense ke MPS ho tsamaisa mekgwatshebetso ha feela:

- Ba boloka mekgwatshebetso ya prothokhole ya phuputso.

- Ba boloka melao ya Medicines Control Council le ya Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC).
- Ba tshwara le ho fana ka moriana wa phuputso ho latela prothokhole le dihlomathiso le ditokomane tse ding tse amanang le yona.
- Ho tloswa qosong ya molato ha ho a rerelwa mme ha ho nka sebaka sa inshorense ya motho bakeng sa ketso efe kapa efe e mpe.

Ka kopo lemoha hore haeba o na le pholisi ya inshorense ya bophelo o tshwanetse ho botsa haeba khamphani ya hao ya inshorense e hloka hore e tsebiswe mabapi le ho nka karolo ha hao phuputsong. Ho tswa tlhahisoleseding e nngwe, sena ha se a lokela ho ama pholisi efe kapa efe ya bophelo eo o e nkileng. Empa ho ntse ho le bohlokwa ho hlahloba hape sena hobane ka dinako tse ding dikhamphani di a fapana.

MOHLODI WA TLHAHISOLESEDING E EKETSEHILENG

Nakong ya phuputso, o tla hlokomelwa ke moifo wa Sepetlele sa South Rand. Haeba ka nako efe kapa efe o nahana hore o na le dipotso tse eketsehileng tse amanang le phuputso, ka kopo iteanye le nna kapa mooki wa phuputso/mohokahanyi ya leng mosebetsing sepetlele.

Litho (Bafuputsi le Bafuputsi ba Tlasana) tsa phuputso tseo o ka iteanyang le tsona:

- ✓ Cara Hollander – 082 815 8878 (Ngaka e hlahlobang kutlo ditsebeng)
- ✓ Ngaka Karin Joubert – 011 717 4561 (Ngaka e hlahlobang kutlo ditsebeng)
- ✓ Moprofesara Natalie Schellack – 012 521 3286 (Rakhemisi)
- ✓ Ngaka Shilubane – 011 681 2184
- ✓ Ngaka Mohammed Rassool –011 276-8813 (Ngaka le Mofuputsi ya ka Sehloohong)

- Haeba o batla tlhahisoleseding efe kapa efe mabapi le **ditokelo tsa hao jwaloka monkakarolo phuputsong, kapa o na le ditletlebo mabapi le phuputso ena,** o ka iteanya le Moprofesara Cleaton-Jones, Modula-setulo wa Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC), e leng komiti e ikemetseng e thusang ho sireletsa ditokelo tsa bankakarolo phuputsong mona (011) 717 2301.
- Bakeng sa **tlhahisoleseding ya phuputso** o ka iteanya le mohokahanyi wa Phuputso – Cara Hollander ho tswa Yunivesithing ya Witwatersrand mona 082 815 8878.

LEKUNUTU

- Tlhahisoleseding kaofela eo re e bokellang nakong ya phuputso ena, e kenyeletsang direkoto tsa sepetlele, tlhahisoleseding mabapi le wena le tlhahisoleseding ya phuputso e tla bolokwa e le lekunutu le thata. Ke feela ditho tsa moifo wa phuputso, le dingaka tsa hao le baoki ba tla fihlella

tlhahisoleseding ya hao. Tlhahisoleseding efe kapa efe e tla ngolwa dikgatisong tsa saense kapa ntho efe kapa efe e tla hatiswa e ke ke ya ngolwa lebitso la hao.

- Re tla kenya dikhoutu tse fapaneng tlhahisoleseding ya hao ya phuputso. Ka lebaka lena, ha ho hlahlojwa diphetho tsa hao, ho tla ba le khoutu feela. Lebitso la hao, nomoro ya hao ya boitsebahatso kapa dinoutu dife kapa dife tse ding tse ka o tsebahatsang di ke ke tsa kengwa ditokomaneng tsena, ho etsa bonnete ba hore ntho e nngwe le e nngwe e bolokwa e le lekunutu.
- Tlhahisoleseding ena e tla hlahlojwa ke baemedi ba dumeletsweng ba Yunivesithi ya Witwatersrand le Yunivesithi ya Sefako Makgatho Health hammoho le ditho tse tswang ho batshehetsi ba ditjhelete (Medical Research Council). Diodithara tsa Wits Health Consortium di ka sheba diphetho tse itseng ha di etsa tlhahlobo ya tsona ho etsa bonnete ba hore ntho e nngwe le e nngwe e entswe ho latela ditekanyetso tse loketseng. Le ha ho le jwalo, ha se motho e mong le e mong ya tla fihlella lebitso la hao – diphetho tsohle tsa hao di tla kengwa nomoro, kahoo ba ke ke ba tseba hore ke wena.
- Tlhahisoleseding hape e ka hlahlojwa ke National Health Research Ethics Committee (NHREC), Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC), Medicines Control Council (MCC) ya Afrika Borwa le/kapa Food and Medicine Administration (FDA) ya United States hammoho le ngaka ya hao. Ka lebaka lena, o nneha tumello ya ho lokolla direkoto tsa hao tsa bongaka ho di neha Medical Research Council, basebetsi ba bona kapa dienjente, ba boholong ba bophelo bo botle hara naha le dinaheng disele, Medicines Control Council (MCC) ya Afrika Borwa, National Health Research Ethics Committee (NHREC) le Yunivesithi ya Witwatersrand, Human Research Ethics Committee (HREC).
- Direkoto tsena di tla sebediswa ke bona feela ho etsa mesebetsi ya bona e amanang le phuputso ena ya moriana.
- Tlhahisoleseding efe kapa efe e fumanwang e amanang le diphetho tsa diteko tsa hao kapa boemo ba bophelo ba hao bo botle ka lebaka la ho nka karolo ha hao phuputsong ena e tla bolokwa e le lekunutu le thata. O tla bolellwa mabapi le diphumano dife kapa dife tsa bohlokwa bophelong ba hao bo botle kapa ho tswela pele ha hao phuputsong ena empa tlhahisoleseding ena e ke ke ya fuwa motho ofe kapa ofe wa boraro hammoho le batho ba seng ba boletswe mona ka hodimo ntle le tumello ya hao e ngotsweng. Mokgelo feela tabeng ena e tla ba diketsahalong tsa mafu a tshwaetsang moo e leng boikarabelo ba molao ho tsebisa Lefapha la Bophelo bo Botle ka ona. Ketsahalong e jwalo, ke tla o bolella mabapi le sena le hore ke tla neha lekgotla la mmuso le dumeletsweng tlhahisoleseding ena.

KGETHO YA HO TSEBISA NGAKA YA HAO / NGAKA E KGETHEHILENG

Ka kopo mpolelle mona ka tlase, haeba o lakatsa hore ke tsebise ngaka ya hao kapa ngaka ya hao e kgethehileng hore o nka karolo phuputsong ena:

- **E**, ke lakatsa hore o bolelle ngaka ya ka / ngaka e kgethehileng mabapi le ho nka karolo ha ka phuputsong ena.
- **TJHE**, ha ke lakatse hore o bolelle ngaka ya ka / ngaka e kgethehileng mabapi le ho nka karolo ha ka phuputsong ena.
- **Ha ke na** ngaka ya ka / ngaka e kgethehileng

DIPOTSO TSA BANKAKAROLO

Na wena, jwaloka monkakarolo, o na le dipotso dife kapa dife?

E / TJHE

Haeba E – Ka kopo hlalosa.

TUMELLO E BONTSHANG KUTLWISISO BAKENG SA BONKAKAROLO PHUPUTSONG

Ke netefatsa hore ke ile ka hlahiswa leseding ke mooki wa phuputso, ... *(LEBITSO LE FELETSENG)* mabapi le sebopeho, tsamaiso, melemo le dikotsi tsa phuputso e nang le sehlooho "Phuputso e fuputsang kgonahalo ya pharmacokinetics le pharmacodynamics ya kanamycin le capreomycin bakuding ba nang le DR-TB le kamano pakeng tsa ditekanyo tsa ho utlwa ditsebeng" (NOMORO YA PROTHOKHOLE 1.5).

- Hape ke amohetse, ke badile le ho utlwisisa tlhahisoleseding e ngotsweng mona ka hodimo (Maqephe a Tlhahisoleseding ya Monkakarolo le Tumello e Bontshang Kutlwisiso mabapi le phuputso ena ya moriana.
- Ke a lemoha hore diphetho tsa phuputso, ho kenyeletswa le tlhahisoleseding ya ka mabapi le bong, dilemo, letsatsi la tswalo, ditlhaku tse qalang tsa mabitso a ka le tlhahlobo ya bongaka ntle le lebitso la ka e tla etswa tlaleho ya phuputso.
- Ke a lemoha hore ho hlokeha hore ke tle tliliniking ya Helen Joseph bakeng sa dikgwedi tsena tse 3, beke e nngwe le e nngwe.
- Ke a lemoha hore nka ka kgetha ho ya tliliniking ya sebaka sa rona kapa tliliniking ya Helen Joseph letsatsi le letsatsi bakeng sa diente tsa ka mme ke dumela ho etsa jwalo letsatsi le letsatsi.
- Ka lebaka la ditlhokeho tsa phuputso, ke dumela hore tlhahisoleseding e bokellwang nakong ya phuputso ena e ka kengwa sistiming ya khomphutha ke bafuputsi ba amehang phuputsong ena, batshehetsi ba ditjhelete kapa lebitsong la bona.
- Ke dumela ho nka karolo diseteng tse 7 tsa diteko tsa kutlo dikgweding tse 3 tsa pele.
- Ke dumela ho nka karolo diseteng tse 8 tsa diteko tsa madi dikgweding tsena tse 3.
- Ke dumela ho fana ka 2 ml tsa madi ka makgetlo a 2 dikgweding tse 3 tsa pele.
- Ke dumela ho fana ka 4ml tsa madi ka makgetlo a 6 nakong ya phuputso. Le 18 ml tse ding bakeng sa ho etsa ditekanyo tsa ditshebetso tsa diphio dikgweding tse 3 tsa pele.
- Ke a tseba hore nka ikgula phuputsong ka nako efe kapa efe.
- Mohatong ofe kapa ofe, ntle le tshwaro e se nang leeme, nka hula tumello ya ka le bonkakarolo phuputsong.
- Ke bile le nako e lekaneng ya ho botsa dipotso mme (ka bolokolohi) ke bolela hore ke malala-a-laotswe ho nka karolo phuputsong.

- Ke a lemoha hore haeba ngaka ya e fetola moriana wa ka hore e be ntho e nngwe ntle le kanamycin/capreomycin, ke tla tloswa phuputsong.

MONKAKAROLO

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno / Letshwao kapa Kgatiso ya Monwana o Motona	Letsatsi le Nako

MOFUPUTSI YA TLASANA PHUPUTSONG

Nna, ..., ke netefatsa hore monkakarolo ya ngotsweng mona ka hodimo o ile a hlahiswa leseding ka ho feletseng mabapi le sebopeho, tsamaiso le dikotsi tsa phuputso e boletsweng ka hodimo mona.

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

MOFETOLEDI / MOTHO E MONG YA HLALOSANG TUMELLO E BONTSHANG KUTLWISISO (MOFUPUTSI YA TLASANA PHUPUTSONG)

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

PAKI (Haeba e hlokeha)

Lebitso ka Ditlhaku tse Arohantsweng	Tshaeno	Letsatsi le Nako

Appendix G

Baseline Case Report Forms

Kanamycin Study **Clinical HIV Research Unit** **Visit: Baseline (Day 1)**
Visit Date: _____ **(DD.MMM.YYYY)** **Initials:** _____ **Study Number:**

Visit: Baseline (Day 1)

Procedures	Yes	No
Main Informed Consent		
Case History		

	YES	NO
Does the patient qualify to be enrolled on the study?(If no, state reason)		
	CM	
Injectable Prescribed for Participant (please circle): KANAMYCIN / CAPREOMYCIN		

Subjects Medical History:

System	History	Start Date	Stop Date
HEENT **NECK**			
CVS	Hypertension No I__I Yes I__I →		

Respiratory System	TB No I__I Yes I__I →		

Subjects Medical History:

System	History	Start Date	Stop Date
GUT			
UGT / Contraception / Safe Sex Method	LMP No I__I Yes I__I → ↓ Reason:		
	Contraception No I__I Yes I__I *(if yes, specify):*		
	1.		
	2.		

Hematological Conditions			
Rheumatological (MSS)			
Endocrine	DiabetesNo I__I Yes I__I		
CNS			
Dermatology			

System	History	Start Date	Stop Date
Reticulo-endothelial System			
Allergies	Allergy to any medication No I__I Yes I__I→		
	Any allergy to yeast No I__I Yes I__I→		
Other	Are you currently taking any Medication? No I__I Yes I__I→		
	Hospitalization in the last No I__I Yes I__I→ 30 days		
CD4 Count		Date	

Signature/Initials		Date	

Procedures	Yes	No
HIV test (if hospital records is not available)		
Pharmacological		
Peak (4-6 hours after KM/CM)		
Package, Centrifuge and Refrigerate Blood		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Other		
Administer KM/CM (and complete drug diary) (please circle whether KM or CM)		

Visit: Baseline (Day2)

	An Inpatient	An Outpatient
Is the participant?		

Any Interim Medical History ➔

Weight
I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1**
I__I__I**.**I__I **°Celsius**	PR _____/**min**	RR _____/ **min**	Bp _____ / _____ **mm/Hg** **Blood Pressure 2** Bp _____ / _____ **mm/Hg**

Signature/Initials		**Date**	

➔Assessment

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓ I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔Plan

Baseline Audiological Measures

Date admitted to hospital for DR-TB (if at all)	
Time and date of last dose of kanamycin/capreomycin	

Audiology Checklist

	YES	**NO**	
Medication			○Kanamycin ○ Capreomycin ○ ARV ○ High Cholesterol ○ Diabetes ○ Other
Family History of Hearing Loss			
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tympanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – Do Repeated Measures

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Signature/Initials		**Date**	

Signature/Initials		**Date**	

Consistent	**Co-operative**	**Other**

[redacted]

Procedures	Yes	No
Pharmacological		
Trough (30-60 mins before KM)		
Package, Centrifuge and Refrigerate for SMU (with requisition form **AND** drug diary)		
Administer KM/ CM (30 to 60 minutes AFTER trough and complete drug diary) (please circle whether KM or CM)		

Name		**Signature/Initials**		**Date**	

Visit: Baseline (Day3)

	An Inpatient	**An Outpatient**
Is the participant?		

Any Interim Medical History ➔

➔Assessment

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓ I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔Plan

Signature/Initials		**Date**	

Appendix H

Patient Contact Information Form

Patient Contact Information

Please update the patient information sheet as follows:

		√		√	**HOSPITAL** **SR/HJ**
Enrolled to main study?	**YES**		**NO**		
Premature treatment discontinuation?	**YES**		**NO**		
Premature study discontinuation?	**YES**		**NO**		

List of signed consent documents/participant letters:

REASON FOR STUDY/ TREATMENT DISCONTINUATION:	

Language	Version	Version Dated	Consent type (Main, Storage, Participant letter etc.)	Date signed by participant

Telephone contact Update (participants address to be updated on Patient Information sheet):

Initial contact number :

_____

Contact telephone number	Name of designated contact	Date of modification	Update done by - Signature

Appendix I

Week 2: Follow Up Case Report Form

Kanamycin Study **Clinical HIV Research Unit** **Visit: Week 2**

Visit Date: _____ **(DD.MMM.YYYY)** **Initials:** _____ **Study Number:**_____

[redacted]

Procedures	Yes	No
Case Report Form		
Follow-up Case Report		
Pharmacological (Study Coordinator)		
Peak (4 to 6 hours after KM/CM)		
Trough (30 to 60 minutes before KM/CM)		
Creatinine (and send to CLS) (both SR and HJ)		
Package, Centrifuge and Refrigerate (with requisition form AND drug diary)		
Audiology (Study Coordinator)		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Medical (Doctor/PI) (and study coordinator to copy notes for study file)		
Physical Exam		
Other		
Administer KM/CM (complete drug diary) Please circle whether participant on KM or CM		

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight

I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1** Bp _____ / _____ **mm/Hg** **Blood Pressure 2** Bp _____ / _____ **mm/Hg**
I__I__I.I__I **°Celsius**	PR _____/**min**	RR _____/ **min**	

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		

Lower Extremities ***For Oedema***	Normal Abnormal ☐☐		
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

Signature/Initials		**Date**	

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓

I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔**Plan**

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin/capreomycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	

Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	
Discharge from the ears?	
Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	**NO**	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

DPOAE

Please print the DPOAE results and staple them below:

NB – do repeated measures!

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Appendix J

Week 4: Follow Up Case Report Forms

Kanamycin Study **Clinical HIV Research Unit** **WEEK 4**

Visit Date: _____ **(DD.MMM.YYYY)** **Initials:** _____ **Study Number:** _____

[redacted]

Procedures	Yes	No
Case Report Form		
Follow-up Case Report		
Pharmacological		
Peak (4 to 6 hours after KM)		
Trough (30 to 60 minutes before KM)		
Refrigerate, Centrifuge and Package (with requisition form and drug diary)		
Creatinine (and send to CLS) (only at SRH)		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Medical (Doctor/PI)(study coordinator to copy physical exam notes for study file)		
Physical Exam		
Other		
Administer KM/CM (and complete drug diary) Please circle if participant on KM/CM		

Visit:Week 4

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight
I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1**
I__I__I**.**I__I **°Celsius**	PR _____**/min**	RR _____**/ min**	Bp _____ **/** _____ **mm/Hg** **Blood Pressure 2** Bp _____ **/** _____ **mm/Hg**

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		

Lower Extremities ***For Oedema***	Normal Abnormal ☐☐		
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

Signature/Initials		**Date**	

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded?

✓I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>**

updates?✓I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔Plan

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	
Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	
Discharge from the ears?	

Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	NO	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – Do Repeated Measures

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Signature/Initials		Date	

Appendix K

Week 6: Follow Up Case Report Forms

Kanamycin Study **Clinical HIV Research Unit** **WEEK 6**

Visit Date: _____ **(DD.MMM.YYYY)** **Initials:** _____ **Study Number: -**

[redacted]

Procedures	Yes	No
Case Report Form		
Follow-up Case Report		
Pharmacological		
Peak (4 to 6 hours after KM)		
Trough (30 to 60 minutes before KM)		
Creatinine (and send to CLS) (HJH AND SRH)		
Refrigerate, Centrifuge and Package for Medunsa (with requisition form and drug diary)		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Other		
Administer KM/CM (and complete drug diary) Please circle whether participant on KM or CM		

Visit: Week 6

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight
I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1**
I__I__I**.**I__I **°Celsius**	PR _____**/min**	RR _____**/ min**	Bp _____ **/** _____ **mm/Hg**
			Blood Pressure 2
			Bp _____ **/** _____ **mm/Hg**

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		
Lower Extremities	Normal Abnormal ☐☐		

For Oedema			
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

Signature/Initials		**Date**	

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓

I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔**Plan**

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin/capreomycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	
Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	
Discharge from the ears?	

Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	NO	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – do repeated measures!

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Signature/Initials		Date	

Appendix L

Week 8: Follow Up Case Report Forms

Visit: Week 8 Checklist

Procedures	Yes	No
Standard of Care at HJH		
Creatinine (Cr,GRF) (study coordinator to send results to SMU)		
CD4		
Potassium (K)		
Case Report Forms		
Follow-up case Report forms		
Pharmacological		
Peak (4 to 6 hours after KM/CM)		
Trough (30 to 60 minutes before KM/CM)		
Refrigerate, Centrifuge and Package for SMU (with requisition form and drug diary)		
Creatinine (SRH ONLY)		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAEs		
Pure Tone Audiometry		
Medical (Doctor/PI) (study coordinator to copy physical exam results for study file)		
Physical Exam		
Other		
Administer Kanamycin and complete drug diary Please circle whether participant on KM/CM		

Visit: Week 8

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight
I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1**
I__I__I**.**I__I **°Celsius**	PR _____**/min**	RR _____**/ min**	Bp _____ **/** _____ **mm/Hg** **Blood Pressure 2** Bp _____ **/** _____ **mm/Hg**

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		
Lower Extremities	Normal Abnormal ☐☐		

For Oedema			
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

Signature/Initials		**Date**	

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓

I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔**Plan**

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin/capreomycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	

Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	
Discharge from the ears?	
Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	**NO**	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – Do Repeated Measures

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Signature/Initials		Date	

Appendix M

Week 10: Follow Up Case Report Forms

Visit: Week 10 Checklist

Kanamycin Study **Clinical HIV Research Unit**
WEEK 10

Visit Date: _____ **(DD.MMM.YYYY)** **Initials:** _____ **Study Number: -**

_____

Procedures	Yes	No
Case Report Form		
Follow-up Case Report		
Pharmacological		
Peak (4 to 6 hours after KM/CM)		
Trough (30 to 60 minutes before KM/CM)		
Creatinine (send to CLS) (HJH AND SRH)		
Refrigerate, Centrifuge and Package for SMU (with requisition form and drug diary)		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Other		
Administer Kanamycin/Capreomycin and Complete Drug Diary Please circle whether participant on KM/CM		

Visit: Week 10

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight

I__I__I__I. I__I kg

Temperature I__I__I.I__I **°Celsius**	**Pulse** PR _____/**min**	**Respiratory Rate** RR _____/ **min**	**Blood Pressure 1** Bp _____ / _____ **mm/Hg** **Blood Pressure 2** Bp _____ / _____ **mm/Hg**

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		
Lower Extremities	Normal Abnormal ☐☐		

For Oedema			
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

Signature/Initials		**Date**	

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded?

✓I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>**

updates?✓I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔**Plan**

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin/capreomycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	
Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	
Discharge from the ears?	

Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	NO	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – Do Repeated Measures

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Signature/Initials		Date	

Appendix N

Week 12: Follow Up Case Report Forms

Visit: Week 12 Checklist

Procedures	Yes	No
Case Report Form		
Follow-up Case Report		
Pharmacological		
Peak (4 to 6 hours after KM)		
Trough (30 to 60 minutes before KM)		
Creatinine (send to CLS) (HJH AND SRH)		
Refrigerate, Centriguge and Package for Medunsa (with requisition form and drug diary)		
Audiology		
Cerumen Mx (if indicated)		
Case Report		
Otoscopy		
Tympanometry		
DPOAE		
Pure Tone Audiometry		
Medical (Doctor/PI) (study coordinator to copy physical examination and place in study file)		
Physical Exam		
Other		
Administer Kanamycin/Capreomycin and Complete Drug Diary Please circle whether participant on KM/CM		

DISCHARGE AND COUNSEL ABOUT CLINIC PROCEDURES FOR INJECTIONS ETC. AND REFER TO AUDIOLOGY CLINIC IN THEIR DISTRICT

Kanamycin Study	**Clinical HIV Research Unit**	**WEEK 12**
Visit Date: _____ **(DD.MMM.YYYY)**	**Initials:** _____	**Study Number:** _____

Visit: Week 12

	An Inpatient	**An Outpatient**
Is the participant?		

	Not Applicable	**Date of Discharge**
If the participant was an inpatient, and has been discharged:		

Any Interim Medical History ➔

Weight
I__I__I__I**.** I__I kg

Temperature	**Pulse**	**Respiratory Rate**	**Blood Pressure 1**
I__I__I.I__I **°Celsius**	PR _____**/min**	RR _____**/ min**	Bp _____ **/** _____ **mm/Hg**
			Blood Pressure 2
			Bp _____ **/** _____ **mm/Hg**

Targeted Physical Exam:

System	Observations/Findings	Body Site/Specify	Grade
HEENT			
Respiratory	Normal Abnormal ☐☐		
CVS	Normal Abnormal ☐☐		
Abdomen	Normal Abnormal ☐☐		
GUT	**Pelvic exam done** No Yes ☐☐		
Lower Extremities	Normal Abnormal ☐☐		

For Oedema			
MSS	Normal Abnormal ☐☐		
Derm	Normal Abnormal ☐☐		
CNS	Normal Abnormal ☐☐		
Other	No Yes ☐☐		

➔**Assessment**

Are there any previously identified **SIGNS & SYMPTOMS** that are new/resolved/upgraded?✓

I__I no

I__I yes➪

If **Yes**, **complete the Signs/Symptoms** page.

Are there any previously identified **DIAGNOSIS**that are new/resolved/upgraded? ✓

I__I no

I__I yes➪

If **Yes**, **complete the Diagnosis** page

Are there any **CONCONMITANT MEDICATION/<u>TRADITIONAL MEDS</u>** updates?✓ I__I no

I__I yes➪

If **Yes**, **complete the Con Meds** page

➔**Plan**

Signature/Initials		**Date**	

Participant/Case report form

***for all follow up measures after baseline**

Participant Number	
Current Weight	
Date drug therapy was initiated	
Current drug therapy (drug name, dosage and duration of drug therapy)	***See drug diary***
Other illnesses since the previous set of measurements (Date, duration, description)	
Time and date of last dose of kanamycin/capreomycin	
Any behavioural/ emotional/ psychiatric changes reported in the file since the last set of measurements	
Has the participant received kanamycin/capreomycin daily since the last visit? If not, which days did the participant not go to the clinic and why.	
Any hearing changes since the last set of measurement recorded in the file	
Any hearing changes since the last set of measurements as reported subjectively by the participant	
Other significant co-variables reported in the file since the last set of measures	
Tinnitus?	

Discharge from the ears?	
Willingness to continue with current set of measurements (blood and audiological testing)	
Verbal consent to participate in the measures again	
Overall participant compliance with procedures and medication. Describe attitude.	

Audiology Checklist

	YES	NO	
Medication			○ **Kanamycin** ○ **Capreomycin** ○ **ARV** ○ **High Cholesterol** ○ **Diabetes** ○ **Other**
Otalgia (ear pain)			
Ottorhea (Discharge)			
Tinnitus (Ringing or noises in the ear)			
Dizziness			
Aural Fullness			
Hearing Loss			
Noise Exposure			

Audiological Measures

Otoscopy	No abnormalities detected	Cerumen but not occluding No Cerumen = 1 ↓ 70% occluding = 2 ↑70% occluding = 3	Occluding Cerumen	Other (please describe)	Cerumen Removed Via Suction
Right Ear					
Left Ear					

Tymanometry	Type	Ear Canal Volume (ml)	Pressure (daPa)	Compliance (ml)	Gradient (daPa)
Right Ear					
Left Ear					

Signature/Initials		**Date**	

DPOAE

Please print the DPOAE results and staple them below:

NB – Do Repeated Measures

Pure Tone Audiometry

Please print and place pure tone audiometry results here. Please email the results as well.

Consistent	Co-operative	Other

Signature/Initials		Date	

Appendix O

Drug Diary for Hospital Patients

Kanamycin Study	Clinical HIV Research Unit
	Visit:

DAILY DRUG DIARY				
Drug	**Dosage**	**Start**	**Stop**	**Sign**
Moxifloxin	**400 mg**			
Ethionamide	**250 mg** **500 mg**			
Terizidone	**250 mg** **500 mg** **750 mg** **1000 mg**			
Pyrazinamide	**500 mg** **1000 mg** **1500 mg**			
INH	**300 mg**			
Pyridoxine	**25 mg/ 50 mg** **75 mg/ 125 mg** **150 mg** **Other:**			

Appendix P

Daily Drug Diary for Local Clinics

DAILY DRUG DIARY – KANAMYCIN STUDY

Study Coordinator: Matshediso Mkhwanazi: speed dial: 50017/ 076 711 2874 (Helen Joseph TB Focal Point)

DATE	KANAMYCIN (KM) or CAPREOMYCIN (CM) ADMINISTERED	DOSE	TIME OF INJECTION	COMMENTS	NURSE SIGNATURE

Appendix Q

Laboratory Requisition Form to CLS

CT Form 017
EDITION 2

CLINICAL LABORATORY SERVICES

KANAMYCIN STUDY P1253

Clinical Requisition Form

CP NUMBER

CLS PRACTICE NUMBER - 5204240

PARTICIPANT DEMOGRAPHICS

CLS Project Location P1253 (for CLS use only)

Participant ID: | | | | | Initials | | | |

Date of Birth | d | d | m | m | m | y | y | y | y | Gender | M | F |

VISIT SECTION

24 hour Clock		Day		Month			Year			
:										
Time of collection		Sampling Date								

PLEASE MARK VISIT

Day 3 (HIV)				Week 10 (CREAT)	
Week 2 (CREAT)				Week 12 (CREAT)	
Week 6 (CREAT)					

WEIGHT (KG)

Specimen collected by:

NAME:

SAMPLE COLLECTION/TEST REQUEST

					SITE USE	LAB USE		
No	Type of Tube	Specimen type	Sample code	TEST	REQUEST	TEST CODE	TESTING LAB	CLS RECEIVED
1	3.5 ML SST	BLOOD	B	CREATININE		CREAT	CLS	
1	3.5 ML SST	BLOOD	B	HIV		HIVCA	CLS	

3.5 ML SST

ADDITIONAL INFORMATION

SPECIAL INSTRUCTIONS

SITE CONTACT INFORMATION:
P.INVESTIGATOR: Mohammed Rassool
ADDRESS: Clinical HIV Research Unit (CHRU)
Helen Joseph Hospital
Westdene
Study Coordinator : Matshidiso Mkhwanazi
Cel: 076 711 2874 Fax: 011 482 2130

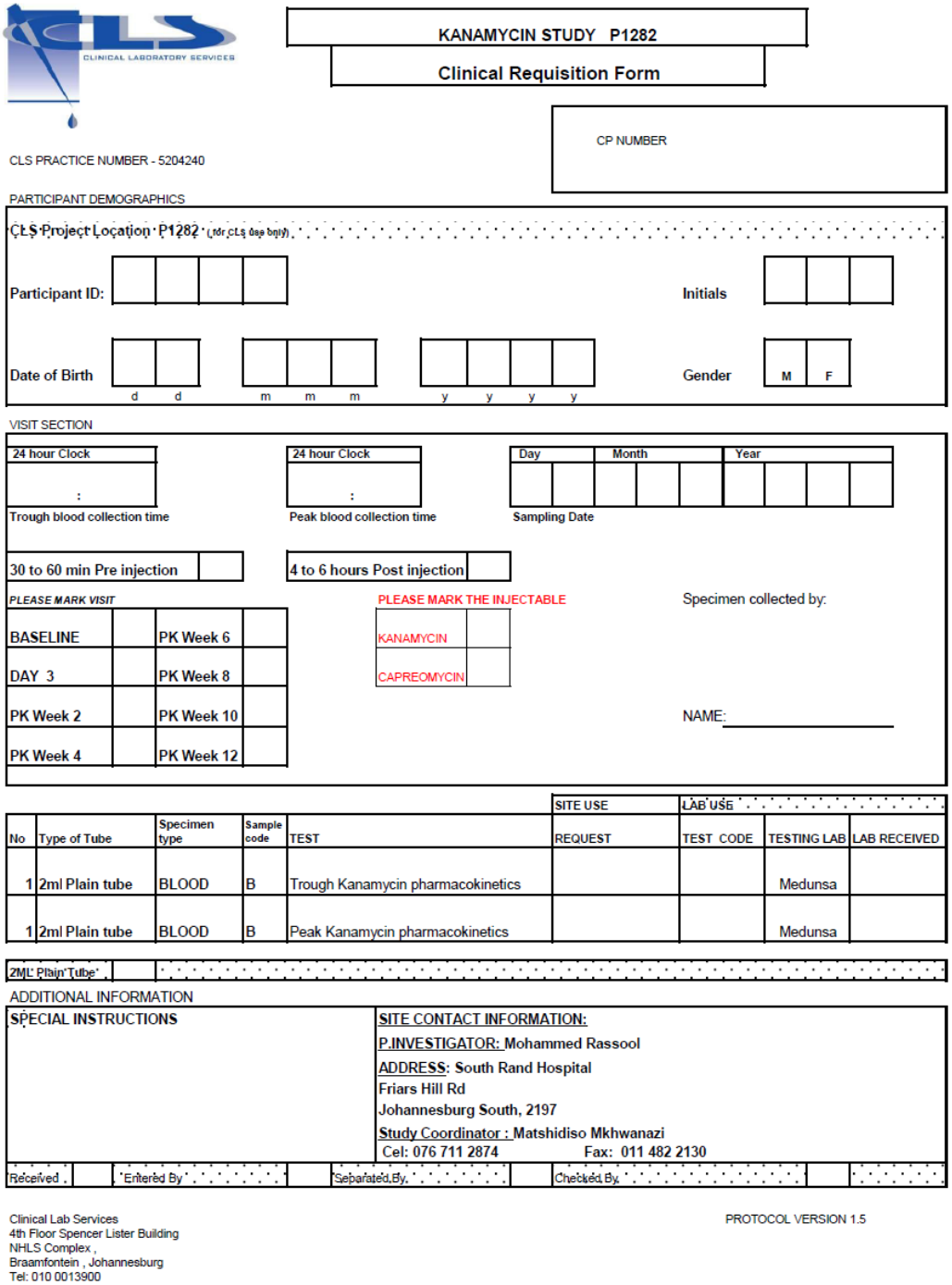
Received | Entered By | Separated By | Checked By

Clinical Lab Services
4th Floor Spencer Lister Building
NHLS Complex ,
Braamfontein , Johannesburg
Tel: 010 0013900

PROTOCOL 1.5

Appendix R

Laboratory Requisition Form for Sefako Makgatho Health Sciences University



CLINICAL LABORATORY SERVICES

KANAMYCIN STUDY P1282

Clinical Requisition Form

CLS PRACTICE NUMBER - 5204240

CP NUMBER

PARTICIPANT DEMOGRAPHICS

CLS Project Location P1282 (for CLS use only)

Participant ID:

Initials

Date of Birth d d m m m y y y y

Gender M F

VISIT SECTION

24 hour Clock	24 hour Clock	Day	Month	Year
:	:			
Trough blood collection time	Peak blood collection time	Sampling Date		

30 to 60 min Pre injection		4 to 6 hours Post injection	

PLEASE MARK VISIT

BASELINE		PK Week 6	
DAY 3		PK Week 8	
PK Week 2		PK Week 10	
PK Week 4		PK Week 12	

PLEASE MARK THE INJECTABLE

KANAMYCIN	
CAPREOMYCIN	

Specimen collected by:

NAME:_____

					SITE USE	LAB USE		
No	Type of Tube	Specimen type	Sample code	TEST	REQUEST	TEST CODE	TESTING LAB	LAB RECEIVED
1	2ml Plain tube	BLOOD	B	Trough Kanamycin pharmacokinetics			Medunsa	
1	2ml Plain tube	BLOOD	B	Peak Kanamycin pharmacokinetics			Medunsa	

2ML Plain Tube

ADDITIONAL INFORMATION

SPECIAL INSTRUCTIONS

SITE CONTACT INFORMATION:
P.INVESTIGATOR: Mohammed Rassool
ADDRESS: South Rand Hospital
Friars Hill Rd
Johannesburg South, 2197
Study Coordinator : Matshidiso Mkhwanazi
Cel: 076 711 2874 Fax: 011 482 2130

Received | Entered By | Separated By | Checked By

Clinical Lab Services
4th Floor Spencer Lister Building
NHLS Complex ,
Braamfontein , Johannesburg
Tel: 010 0013900

PROTOCOL VERSION 1.5