

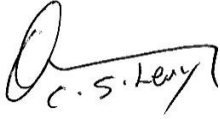
AN ECONOMIC EVALUATION OF THE
ESTABLISHMENT OF A PAEDIATRIC DIALYSIS UNIT
AT PIETERSBURG HOSPITAL, POLOKWANE,
LIMPOPO

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A Dissertation submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree
of Master of Public Health.

Johannesburg, July 2024

I, Cecil Steven Levy, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Public Health at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

A handwritten signature in black ink, appearing to read 'C. S. Levy' with a stylized flourish at the end.

(Signature of candidate)

22nd day of July 2024, in Johannesburg

This Dissertation is dedicated to my parents, to my wife, and to my daughters.

It is also dedicated to the children I have been privileged to care for over the years.

PUBLICATIONS AND PRESENTATIONS

There have not yet been any publications or presentations of the data from this study.

ABSTRACT

Introduction: Many children who develop end stage kidney disease in South Africa are denied therapy due to their distance from the hospital. Decentralising paediatric nephrology services would go a long way to relieving the burden on these children and their families. Pietersburg Hospital, Polokwane, has the potential to house a paediatric satellite dialysis unit, but some understanding of the costs and benefits of such a program is needed before it is implemented.

Methods: A cost utility analysis was performed using Markov modelling techniques to analyse the expected costs and benefits of such a program from both the societal and the healthcare payer perspectives. The cost effectiveness was evaluated by analysing incremental cost effectiveness ratios (ICER) and incremental net monetary benefits generated by the analysis. All cost data was obtained from a cohort of children receiving chronic kidney replacement therapy (dialysis and/or kidney transplant) at the Nelson Mandela Children's Hospital (NMCH) between 1 April 2019 and 31 March 2022. The comparator was represented by data from children whose home address was more than 150 km from NMCH, and from a group of "Unstable Kidney Transplant" patients, while the intervention was the theoretical establishment of a satellite paediatric dialysis unit at Pietersburg Hospital, Polokwane, represented by data from children whose home address was less than 150 km from NMCH, and from a group of "Stable kidney transplant" patients.

Results: The deterministic sensitivity analysis predicted that the intervention would be cost effective from both the societal and the healthcare payer perspectives and showed that length of stay resulted in the largest change in the ICER. The probabilistic sensitivity analysis also predicted that the intervention would be cost effective from both the societal and the healthcare payer perspectives. The cost effectiveness acceptability curves demonstrated that the intervention was likely to be cost effective more than 50% of the time for a willingness to pay threshold of ZAR 112 000 (or one times the average gross domestic product per capita for South Africa in 2022).

Conclusion: Our findings are in conformity with data from the literature which show that satellite dialysis units can be cost effective. Establishing a satellite unit at Pietersburg Hospital, Polokwane for the treatment of children with end stage kidney disease in the area would not

only improve access and quality of life for these children, but it is also likely to be cost effective, from both the societal and the healthcare payer perspectives. We hope that these findings will encourage the introduction of, at least, a pilot program at Pietersburg Hospital, Polokwane to establish the validity of our results. Success with this model could then be used as a template to roll out similar projects across the region.

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LIST OF ABBREVIATIONS

ABC	Activity Based Costing
CA\$	Canadian Dollars
CAKUT	Congenital Anomalies of the Kidney and Urinary Tract
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CET	Cost Effectiveness Threshold
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence Interval
CKD	Chronic kidney Disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPI	Consumer Price Index
CUA	Cost Utility Analysis
DGMAH	Dr George Mukhari Academic Hospital
DSA	Deterministic Sensitivity Analysis
EE	Economic Evaluation
ESKD	End Stage Kidney Disease
FTE	Full Time Equivalent
GDP	Gross Domestic Product
HALY	Health Adjusted Life Year
HD	Haemodialysis
HRQoL	Health Related Quality of Life
HSU	Health State Utility
HTA	Health Technology Assessment
HUI2	Health Utilities Index Mark 2
HUI3	Health Utilities Index Mark 3
IALCH	Inkosi Albert Lethuli Central Hospital
ICER	Incremental Cost-Effectiveness Ratio
Int\$	International Dollars
ISPOR	The Professional Society for Health Economics and Outcomes Research
KDIGO	Kidney Disease: Improving Global Outcomes

KRT	Kidney Replacement Therapy
KT	Kidney Transplant
KZN	Kwa-Zulu Natal
LOS	Length of Stay
MAUI	Multi-Attribute Utility Instrument
MH	Marang House
NHLS	National Health Laboratory Services
NMB	Net Monetary Benefit
NMCH	Nelson Mandela Children's Hospital
NPV	Net Present Value
PC	Pharmacy Cost
PD	Peritoneal Dialysis
PH	Pietersburg Hospital
pmarp	Per Million of the Age-Related Population
PPP	Public Private Partnership
PRO	Patient Reported Outcomes
PSA	Probabilistic Sensitivity Analysis
PTO	Person Trade-Off
QALY	Quality Adjusted Life Year
RCWMCH	Red Cross War Memorial Children's Hospital
SANBS	South African Blood Transfusion Services
SBAH	Steve Biko Academic Hospital
SD	Standard Deviation
SE	Standard Error
SF-6D	Short Form 6D
SG	Standard Gamble
SR	Systematic Review
TTO	Time Trade-Off
UAH	Universitas Academic Hospital
UK	United Kingdom
USA	United States of America
US\$	United States Dollars
VAS	Visual Analogue Scale

VBA	Visual Basic Application
VSL	Value of a Statistical Life
WHO	World Health Organisation
WTP	Willingness To Pay
ZAR	South African Rand

CHAPTER ONE

INTRODUCTION

This chapter discusses the background to the study and explains the reason for undertaking the study. It then delivers a literature review of the methods of economic evaluation as they apply to the management of end stage kidney disease in general, and to paediatric end stage kidney disease in particular. It ends with an explanation of the rationale behind using data from the Nelson Mandela Children's Hospital for the study.

1.1 Background

Many children who develop end stage kidney disease (ESKD) in South Africa often do not get referred to tertiary units for treatment (1), and many children who do get referred to one of the public sector academic-hospital paediatric nephrology units across the country are denied therapy due to their distance from the hospital (2). The result is the inevitable and traumatic premature death of a child (3). Decentralising paediatric nephrology services would go a long way to relieving the burden on children with ESKD and their families (4).

Polokwane, the capital of Limpopo province, is South Africa's largest urban centre north of Gauteng and is situated 320 km from Johannesburg, almost halfway between Gauteng and the Zimbabwe border (5). Pietersburg Hospital (PH), situated in Polokwane, is a tertiary public sector academic hospital that has the potential to house a paediatric satellite dialysis unit by allowing children access to the existing adult dialysis unit at the hospital. This adult dialysis unit was initially run as a public private partnership (PPP), and was then subsequently taken over by the public service (6). It continues to provide life-saving care to adult patients in the region (6). In addition, a paediatrician currently employed at PH has been earmarked to undergo part time training in paediatric nephrology, and to oversee the management of paediatric nephrology at PH (personal communication with the Head of Paediatrics at PH).

The Nelson Mandela Children's Hospital (NMCH) in Johannesburg hosts a state-of-the-art paediatric dialysis centre (7), and one of the unit's aims is to improve access for rural children to tertiary ESKD care.

Establishing a satellite chronic CRT service at PH would allow children who live closer than 150km to PH to receive their care, under the guidance of the unit at NMCH, at PH rather than at NMCH as is currently the case.

This dissertation examines the estimated costs and benefits of the hypothetical establishment of a satellite dialysis unit for children with ESKD at PH. The model proposes that children from PH with ESKD in need of kidney replacement therapy (KRT) would be referred to NMCH for evaluation. Those deemed fit for treatment would be initiated on dialysis at NMCH and listed for kidney transplantation on the NMCH kidney transplant (KT) list. Once stable on dialysis, they would then be transitioned back to the hypothetical satellite unit at PH for follow up and treatment, and to await their transplant call up. Patients called up for a KT would have their transplant at NMCH and then, once stable, would also be referred to PH for long-term follow up under the direction of the team at NMCH.

The challenge is that the state has limited resources, and alternative uses for these resources are many. Therefore, the establishment of expensive therapies, like paediatric dialysis units, should not be undertaken without some understanding of the costs and benefits that might occur as a consequence of the introduction of such therapies (8).

1.2 Research question, study aim, and the objectives

The research question of the study was as follows: For paediatric patients referred to PH with ESKD in need of KRT, would it be cost effective to establish a satellite paediatric dialysis centre at PH from the viewpoints of both the healthcare payer, in this case the management of PH and the Limpopo Department of Health, and society?

The study aim was to determine the cost effectiveness of establishing a paediatric dialysis unit at PH, with the Limpopo Department of Health and PH management as the target audience.

The comparator was the current situation, in which paediatric patients referred to PH with ESKD in need of dialysis therapy are referred to tertiary hospitals in Pretoria or Johannesburg for evaluation and, if deemed suitable, for long term treatment based at those hospitals. NMCH was assumed to be the tertiary hospital for the purposes of the model. ***This group was represented by data from children treated at NMCH with HD or PD and whose home address was more than 150 km from NMCH, and by a group of “Unstable KT” patients also treated at NMCH.***

The intervention was the theoretical establishment of a satellite paediatric dialysis unit at PH that would be able to care for children already established on chronic KRT by NMCH. The model analysed the costs incurred and the QALYs gained if the paediatric patients referred to PH with ESKD in need of dialysis therapy that had then been referred to, evaluated by, accepted onto, and then established on, the long-term KRT program at NMCH, would then be sent back to PH for their long term KRT until they received a KT. Once transplanted successfully, they would be sent back to PH for long term follow up under the guidance of the team at NMCH. ***This group was represented by data from children treated at NMCH with HD or PD and whose home address was less than 150 km from NMCH, and by a group of “Stable KT” patients also treated at NMCH.***

The specific objectives of the study were as follows:

Objective 1: To establish the expected direct and indirect costs incurred, in both arms of the study, in treating children with ESKD from the PH referral area.

Objective 2: To establish the expected effectiveness of both arms of the study in terms of the quality adjusted life years (QALYs) gained by treating children with ESKD from the PH referral area.

Objective 3: To estimate an incremental cost effectiveness ratio (ICER) comparing establishing, and running, a paediatric dialysis unit at PH to the current state of no paediatric dialysis facility at PH as the counterfactual.

1.3. Literature review

1.3.1 Chronic kidney disease in children and statement of the problem

Chronic kidney disease (CKD) is a public health problem worldwide, and more than two and a half million people are on maintenance dialysis worldwide (9). CKD is defined as “abnormalities of kidney structure or function, present for more than three months, with implications for health”, and a standard staging system for CKD has been formulated (10). This staging system is used for research, clinical practice, and public health (11). In the literature, the incidence, prevalence, and prognosis, for CKD are usually given within the context of this classification system (11). The system divides CKD into five broad groups (Stages 1-5), with CKD Stage 5 being ESKD (10).

Life is not possible for people with ESKD without KRT through either dialysis or kidney transplantation and, in 2010, between two million and seven million people (including perhaps almost 50 000 children), mainly from low- and middle-income countries, lost their lives prematurely because they could not access lifesaving KRT (9).

The most common causes of ESKD in European children are renal hypodysplasia with urinary tract malformations (53%) and hypodysplasia (13%), often associated with primary vesicoureteric reflux (VUR) (25.8%) (12). In South African Black children, common causes of ESKD include nephrotic syndrome associated with focal segmental glomerulosclerosis in up to 46% of cases, congenital anomalies of the kidney and urinary tract (CAKUT) in around 30% of cases, and a congenital type of nephrotic syndrome in up to 13% of cases (13)(14).

CKD is estimated to have an overall worldwide prevalence of between eight and 16 percent, but the disease is much less common in children than it is in adults (15). In Europe, the incidence of childhood CKD is around 11-12 per million of the age-related population (pmarp) per annum for CKD Stages 3-5, and around eight pmarp per annum for Stages 4-5 (11). The prevalence of CKD ranges from 55–75 pmarp, depending on the clinical definition of CKD used (11). The true incidence and prevalence of CKD in South Africa is unknown (16) but the incidence of paediatric CKD in Kwa-Zulu Natal (KZN) has been estimated as being only around one to two pmarp per annum, with a prevalence of 43.7 pmarp (1). However, in South

Africa it is suspected that missed diagnoses, under-referral, and death before reaching a tertiary centre, contribute to these reportedly low numbers (1)(15).

There are gross inequities in the ability of patients from low- and middle-income countries to access medical care in general, and KRT in particular (9)(17)(18). In South Africa, the constitution states that “every person has the right to have access to health care services” (19), but unpublished data suggests that less than 10% of children who need KRT in South Africa are able to access this therapy (20). A combination of poor primary health care, and the insidious progression of ESKD, leads to children commonly seeking health care only once they are already in need of urgent dialysis (15). In these cases, inability to access lifesaving KRT is inevitably fateful within days, if not hours, of presentation (3).

Many reasons have been given to explain this inability to access care, but large distances from tertiary centres, and high travel costs, especially for patients from rural areas, are commonly cited (18)(21). Unfortunately in South Africa, using reasons such as ‘distance from hospital’ to rationalize the selection process for dialysis has often resulted in the denial of therapy to those very communities who were disadvantaged, and discriminated against, in the past (2)(22)(23).

Even though KRT is life saving for patients with ESKD it is expensive, and long-term survival rates and health related quality of life scores for children treated for ESKD remain below those of healthy children (24)(25). While receiving a KT will be beneficial for patients with ESKD in terms of quality of life, survival, and cost (24)(26), for many people transplant options may be limited and financially inaccessible (2)(22)(27)(28). In these cases, dialysis offers a life-extending, but expensive, option (29)(30)(31)(32)(33).

There are two main forms of dialysis, haemodialysis (HD) and peritoneal dialysis (PD) (10). In South Africa, as in other countries, HD is usually performed in a hospital based dialysis unit three times a week whereas PD is performed by the patient, or their caregivers, at home and only requires monthly outpatient review at a dialysis unit (10)(33)(34). The three times a week HD schedule means that children treated on this mode need to live close to the treating centre (20). Due to a worldwide shortage of paediatric specific dialysis units, children are more often than not dialysed in adult facilities, rather than in designated paediatric dialysis centres (35).

It can take a long time to establish a child on one of the modes of KRT and this, combined with the complicated nature of the ESKD, can result in multiple hospital admissions, highlighted by prolonged length of stay (LOS), especially for those children who are from a low socioeconomic background and / or come from far away (20)(36)(37).

While it is acknowledged that medical foster care can provide advantages for children with complex medical conditions who live far away from their treating facility (38), having to live away from home can have a negative impact on their sense of well-being and quality of life (39). In Johannesburg, a registered Section 21 (non-profit) Organization called Marang House (MH) has been life-saving for many patients by giving them a place to stay while they await a KT (40).

A common thread running through the many reasons for the inequities present in accessing tertiary renal care is that resources are finite and, especially in low- and middle-income countries, they are often scarce (18)(41). Issues such as providing basic sanitation and nutrition, and controlling infectious diseases such as malaria, tuberculosis, and HIV/AIDS, tend to take priority over the treatment of CKD (4)(30)(41). Also, in most developing nations, KRT programs are in urban areas while many patients live in rural areas, further limiting the access to dialysis for large sections of the population (4)(41)(42)(43). One solution that has been proposed to improve access to specialised care for patients from rural areas is decentralisation of care (4).

Patients cared for in satellite centres tend to have higher quality of life, as well as less hospitalization and adverse events, than those dialysed in units further away from where they live (44)(45)(46). However, although satellite dialysis units improve access for people who live at a distance from tertiary centres (44)(45) and have been found to be cost effective (47)(48), especially from the societal perspective (49), this might not always be the case from the healthcare payer's perspective (50).

1.3.2 Economic evaluation

The scarcity of resources, such as facilities, equipment, knowledge, personnel, and time, implies that hard decisions need to be taken when deciding on how best to distribute these

scarce commodities (51). The introduction of any new intervention should not be undertaken without an analysis of the costs and benefits, or consequences, that might result because of the potential costs involved (51).

Drummond *et al* explain that this analysis needs to be a formal and systematic process for a number of reasons (51). It would allow for the clear identification of the relevant alternatives, and it would facilitate taking account the viewpoints or ‘perspectives’ of the beneficiaries of the new program as well as of the healthcare payers (51). It would also allow for the estimation of the ‘opportunity cost’ (the benefits that will be foregone from another program should the program under evaluation be implemented), and it would increase accountability for decisions taken (51). This process of comparing the costs and the consequences (benefits or otherwise) of two or more health care interventions is known as economic evaluation (EE) (51).

Stated more formally, Drummond *et al* define EE as “*the comparative analysis of alternative courses of action in terms of both their costs and their consequences*” (51). By using a comparative analysis of two alternative courses of action, in terms of both their costs and their consequences, an economic evaluation allows us to evaluate whether scarce resources should be spent on a particular program or not, and whether it provides good value for money (51). In South Africa, as elsewhere, it is recommended that local data be used wherever possible in order to make the results relevant to the local population (52).

To encourage the standardised reporting of EE in health care, the first Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was published in 2013 (53). The statement listed the recommended minimum amount of information to use when designing and reporting EEs around health-related issues (53). It was designed to help researchers to provide accurate information on the interventions being compared (53). It was also designed to aid researchers to systematically explain the context, methodology, and the findings, of their research, in such a way that they would be of practical use to other researchers, readers, and policy makers (53).

The first CHEERS statement has now been updated and replaced by the CHEERS 2022 statement (54). The updated version is felt to be more broadly applicable than the previous statement, and it is recommended that health EE researchers design their studies around the updated guideline in order to improve healthcare decision making and expenditure (54).

There are several different types of EEs but, while all will measure their costs in monetary terms, they differ in the way in which their consequences are reported (55). The Cost-Benefit Analysis (CBA) reports health benefits in monetary terms (51), but it is difficult to quantify health in this way (55). The Cost Effectiveness Analysis (CEA) focuses on a single health effect of interest common to both the alternatives being evaluated (51). The Cost Utility Analysis (CUA) uses a generic measure of health gain for its consequences (50).

In health economics two types of efficiencies can be addressed by using an EE (56). These are allocative and technical efficiency (56). Allocative efficiency deals with the allocation of resources to different groups of people, with different health problems, to get the best value for money for society, whereas technical efficiency deals with how best to distribute resources amongst patients with the same medical problem in order to try to maximize health gains for that patient group within a given budget (56). While the CEA allows one to evaluate technical efficiency, because it only evaluates the two programs in terms of a single common effect that may differ in magnitude between them, it does not address allocative efficiency (51). On the other hand a CUA, by producing a generic outcome measure, allows one to compare the costs of the benefits of one program with those of an unrelated program, and so addresses questions of both technical, and allocative efficiency (51).

The generic outcome measures which are used to estimate the potential benefit of an intervention in CUAs are derived in each case by multiplying the values estimated for the level of quality of health generated by a certain state of health, by the life expectancy of the patient in that condition, to produce a health adjusted life year (HALY) (57). These HALYs allow for the impact of morbidity and death to be considered simultaneously, and thereby allow for comparisons to be made across a wide spectrum of diseases, medical interventions, and patient populations (57).

1.3.2.1 Health gain

HALYs, DALYs, and QALYs

The morbidity (quality of life) component of the HALY is termed the health-related quality of life (HRQoL), and by convention is expressed on a scale of zero to one (57). When combined with the average length of time a person in that health state could be expected to live, we can

estimate either the disability-adjusted life years (DALYs) associated with specific diseases burdens in different populations, or the quality-adjusted life years (QALYs) of multiple differing health conditions and outcomes (57).

DALYs can be considered a measure of a health gap (a “*bad*” to be minimised), while QALYs are a measure of health expectancy (a “*good*” to be maximised) (57). Therefore, on the DALY scale, zero represents complete health, while 1.0 represents death, and on the QALY scale 1.0 represents complete full health, while zero represents death (57). It is important to note that the health scales used in each system are regarded as having interval scale properties, implying that changes of equal amounts occurring anywhere on the scale are interpreted as if they were equivalent to each other (57).

The HRQoL weights used in each system reflect preferences that people have demonstrated for different states of health based on trade-offs in desirability of the different impacts of illness or disease (57).

Because of difficulties in collecting comparable primary data regarding these preferences from multiple countries, and because self-assessments of health experience vary across cultures, DALYs have their estimates of HRQoL attached to specific diseases, rather than to health states, and experts are used, using a person trade-off (PTO) method followed by deliberation, to assign the DALY weights to various conditions (57). The disadvantage of this approach is that using experts, rather than average members of society, to derive the weights does not make the weights truly representative of general society (57). In addition, by focussing only on a specific health outcome, the health impact of comorbid conditions on the patient’s wellbeing, cannot be captured (57). On the other hand, the QALY measure of health is based on domains of health, rather than on descriptions of diseases or disability, and so QALYs are much more useful when there is a need to quantify, value, and compare, different treatment combinations to determine which one provides the largest societal benefit, welfare, or utility, for any given budget (57)(58).

Utilities

Utilities are values which reflect the quality of an individual’s health state, and can be regarded as the preference, or value, people will demonstrate for a given state of health (59). The greater

the preference for an outcome, the higher the utility that is associated with that preference (60). In welfare economics, the primary goal of resource allocation is to maximise the aggregate of all individual's utilities (57). This aggregate, the social utility function, fits in with utilitarianism, a social theory which suggests that any policies which aim to improve social welfare should do the greatest good for the greatest number of people (57). There are two main approaches used to derive these utilities in such a way that best describe society's views on health (60). These are direct measurement techniques, and the use of multi-attribute systems (61).

The most frequently used direct measurement techniques are the visual analogue scale (VAS), the time trade-off (TTO), and the standard gamble (SG) (61). These methods are preference based in that subjects are asked to provide utilities for the health states of interest which may vary from their own, or someone else's, perspective, and might reflect a hypothetical, or their own, state of health (61). They differ in that the VAS method is a ratings-based method, in which the subject is requested to plot the state of health they are asked to describe onto a rating scale and, from where they place their choice, the researcher will derive their utility or preference for that health state (61). The TTO and the SG are choice-based methods (61). Most researchers feel that choice-based questions are easier for subjects to understand (62), and therefore, because the TTO and the SG ask choice-based questions, they are considered to hold an advantage over the ratings-based VAS (61).

Because direct measurement techniques are complex and time consuming, preference based multi-attribute systems, which are simpler to use, have been developed to obtain valid health outcome utility scores (61). Common examples of these preference based multi-attribute utility instruments (MAUIs) include the EQ-5D (63), the Short Form 6D (SF-6D) (64), the Health Utilities Index Mark 2 (HUI2) (65), and the Health Utilities Index Mark 3 (HUI3) (66)(67).

Multi-attribute utility instruments

MAUIs are all made up of two main parts; a multi-attribute descriptive health status classification system, and a preference-based scoring formula or algorithm for valuing the health states described by the health status classification system (61). The health status classification systems are made up of a group of important functional domains, or attributes of health, such as pain, discomfort, emotion, cognition, and ambulation (60)(61). These differ

between the various instruments as decided upon by the developers of the instruments, and are divided into several levels for each attribute, ranging from complete function to complete dysfunction (57).

While multi-attribute systems use models constructed using direct preference measurement data from random samples of people in the general population, they all differ in which method (TTO, SG, VAS, or some other choice-based method), and which population, were used to elicit the preferences (61). For example; the EQ-5D preferences were obtained using the TTO technique on a random sample of 3000 adults in the United Kingdom (UK) (68)(69), the SF-6D preferences were obtained using the SG technique on a random sample of 836 adults, also from the UK (64), the HUI2 preferences were measured using a VAS technique and a SG instrument on a random sample of parents of school children in Hamilton, Canada (66), while the preferences for HUI3 were measured using the VAS technique and the SG technique on a random sample of adults from that same city (67)(70). Statistical modelling methods are then used to create the scoring algorithm that will allow estimation of values for all the possible health states defined by the instrument (71).

Because the various instruments vary in so many different aspects (72), researchers take several factors into consideration before selecting an instrument to use (60). These include the credibility of the instrument, the relevance of the health status classification system for the population being studied, and the requirements of the audience for which the study is being performed (60). In addition, it is important to consider whether the preferences reported from the particular populations used to score the instruments reflect those of the group under study, and so scores have been developed for different geographical areas across the world (60)(73).

Utilities scores and children

Due the relative lack of good primary utility data for childhood health states, researchers have applied health utility values derived for adults to childhood health states (74). The problem with this approach is that methodological issues are likely to reduce the suitability of adult derived utility values for childhood health states, and so it may be more appropriate to rather use child and adolescent, rather than adult, derived MAUIs when applying interventions that will be targeting these age groups specifically (75).

As reviewed by Rowan *et al* (76), and elaborated upon by Devlin *et al* (77), there are a number of issues that should be taken into account when deciding on the validity of QALYs obtained by using child specific MAUIs; Children may perceive the impact of ill health on various aspects of daily living differently to the way adults do. Also, while self-reporting may be appropriate for older children, it is not feasible for very young children and those children with developmental or learning difficulties. Even when children can fill out structured questionnaires (called “patient reported outcomes” or PROs), the answers given by them are very dependent on how they understand the PRO questions.

In addition, if parents, caregivers, or medical professionals are used, the reliability of the answers will depend on their accurate perception of the child’s experience of their own health. Values for paediatric PROs obtained by asking adults to imagine the health problems of one age group may not be applicable to children who are younger or older and, when modelling the lifetime benefits of an intervention, it may be more accurate to switch to adult values after several years than to stick to the values allotted to the age group of the MAUI. Finally, there is no clarity on whether QALYs gained by children should be worth more than those gained by adults (76)(77).

An ISPOR (The Professional Society for Health Economics and Outcomes Research) task force recommended that child-reported measures be used when children in the target range can complete the PRO independently and, that when informant-based measures are used, the instrument assesses observable content as much as possible rather than rely on subjective interpretations of the child’s experience (78). However, a recent review of the psychometric performance of a selection of child and adolescent-specific MAUIs found that although the EQ-5D-Y-3L, followed by the CHU9D, had the best evidence of good psychometric performance, there were still concerns highlighted about the comparability of self-reported PROs and proxy responses when measuring HRQL of children and adolescents (79). In addition, Kwon *et al* found that the use of parents as proxies led to an overestimation of HUI3 utility scores, implying that parents may underestimate the impact of the less observable aspects of child health, such as emotional and social wellbeing, on their own child’s HRQoL (80). In South Africa, a HRQoL study on children with CKD also found that parents estimated higher levels of HRQoL than those reported by their children in most domains of the Pediatric Quality of Life Inventory (PedsQL 3.0) (81).

While the HUI2 and HUI3 are intended for use in both children (ages 5 years and above) and adults (71), there are several other generic MAUIs that have been designed for use specifically in paediatric and adolescent populations (71)(76). These include the 16D (ages 12-15 years) (82), the 17D (ages 8-11years) (83), the CHU9D (ages 4-17years) (84), the EQ-5D-Y (ages 4-15 years) (85), and the AHUM (ages 12-18years) (86). Within this group, the AHUM can also be applied to adult populations (71). Again, these instruments differ in the methods and populations used to elicit the preferences (71). The 16D was developed using a VAS on 213 schoolchildren from Finland aged 12-15 years (82), the 17D was also developed in Finland using a VAS on 115 parents of children (83), the CHU9D (UK) used a SG technique on adults aged around 49 years (84), and the AHUM (UK) used a TTO technique on 312 UK adults (86).

Despite the availability of these tools, time and resource constraints will often limit the ability of researchers to generate original health utility data for the health conditions of interest (80). In these cases, one of the recommendations made by methodological guidance documents is that analysts resort to the published literature for health utilities (87).

With this in mind, and to correct methodological limitations of previous attempts to review health utility values for childhood health conditions, Kwon *et al* carried out a systematic review (SR) and meta-analysis to generate reliable paediatric utility values from paediatric CUAs, in order to inform paediatric health care decision making (80). They identified and extracted data from 272 studies, published before 31 December 2015, on health utilities for paediatric health states (80). The results yielded utility scores from just over 1000 main samples covering 101 ICD-10 health categories (80). The VAS was the most frequently used direct method, while the HUI3 was the most used indirect valuation method (80). Half of the samples evaluated health states for children under the age of 12 years and, of these, over two-thirds used an adult proxy as the respondent (80). Most of the samples came from the first world setting, and only 255 came from developing countries (80).

From these papers, they reported the mean utility or VAS scores and their associated distributions (80). In addition, in order to derive the VAS or utility scores of each health condition relative to that of the health of the general population, they also performed a meta-regression on the studies that used the two most common methods used, the HUI3 and the VAS and its variants (EQ-5D VAS and EQ-5D-Y VAS) (80). The results were reported in relation to a baseline constant of 0.876 representing the mean average utility of children from the

general population of developed countries (80). In their review they identified five papers that produced utility or VAS scores for children with CKD (88)(89)(90)(91)(92).

Utility scores and CKD

The EQ-5D-3L, SF-6D, and the HUI2 and HUI3 have all been used across multiple countries to generate health state utilities for adult patients in the different stages of CKD, including transplantation (93)(94)(95)(96)(97). In paediatric patients the 16D (88), the 17D (88)(89), the HUI2 (92), the HUI3 (90)(91)(92)(98), the SF6D (92), and the EQ-5D-Y-3L (99) have been used to generate utilities for this group (80).

Wyld *et al* published a SR and meta-analysis of studies on adult patients with CKD that had either reported utilities directly, or from which utilities could be calculated from SF-36 or SF-12 health surveys (96). Using a TTO method they showed that the mean utility scores were 0.82 (95% CI: 0.74, 0.90) for KT recipients, 0.72 (95% CI: 0.62, 0.83) for PD patients, and 0.69 (95% CI: 0.59, 0.80) for HD patients (96). Because the difference between the PD and HD patient utilities was not statistically significant, in their final analysis they gave them both an equal score of 0.70 (95% CI: 0.62, 0.78) (96). They also reported a score of 0.62 (95% CI: 0.43, 0.82) for a group that they called their conservative care group (96).

Cooper *et al* also carried out a SR examining health state utility (HSU) scores for adult patients with CKD stratified according to CKD stage (93). This review was one of the first on the topic to be conducted in accordance with the 2019 recommendations of the ISPOR task force (93)(100). It was designed to provide an international perspective, and it was carried out with the specific goal of identifying HSU weights that could be used for cost-effectiveness modelling in CKD health technology assessment (HTA) (93).

The SR process identified 17 studies which had no obvious sources of bias, and which met all the recommended HTA selection criteria as per the ISPOR guideline (93). Six of the 17 studies gave utilities for HD patients (101)(102)(103)(104)(105)(106), one gave utilities for HD and PD patients (107), one gave utilities for HD, PD, and KT patients (108), and two gave utilities for KT patients alone (109)(110). Of these, five studies used the EQ-5D-3L (102)(104)(105)(106)(108), three used the SF-6D (101)(107)(111), one used the HUI3 (103), and one used multiple instruments (EQ-5D-3L and HUI3) (110). Two studies were reported

from Canada (102)(104), the USA (103)(110), and China (101)(107) each, two studies were multi-national (105)(106), and one each was reported from the UK (108) and Spain (111). The HSU weights ranged from 0.44 - 0.79 (average 0.66) for patients on HD, 0.53 - 0.78 (average 0.66) for patients on PD, and 0.74 - 0.87 (average 0.76) for those with a functioning KT (93).

As expected, because CKD has a significant impact on HRQoL and health expectancy, average HSUs for patients on dialysis were lower than those who had a functioning KT (93). Also, while HSU weights were lower on average for PD than HD when using the EQ-5D-EL, there was no difference in HSU weights between PD and HD when the SF-6D was used (93). Although this highlights the potential for bias when HSU results from studies using different instruments are used, the true value for the HSUs probably fall within the range of scores reported by the SR (93). This suggests that any CUA performed using these results should be done either by using the range of reported scores rather than just any one single point, or by selecting only the HSUs from one instrument (94). In Cooper *et al*'s SR the average age of the patients was close to 56 years, with the youngest patients close to 40 years of age (93). Very few studies have reported HSUs for children with CKD (80).

Utility scores and children with CKD

Kwon *et al* identified five studies that produced utility or VAS scores for children with CKD (80). One study (88) used the 16D, which uses a tariff derived using a VAS from 213 Finnish schoolchildren aged 12-16 years (82). Two studies (88)(89) used the 17D, which uses a tariff derived using a VAS from 115 Finnish parents of children aged 8-11 years (83). Two papers (91)(92) used the HUI2, which uses a tariff derived using a VAS and a SG technique from 194 Canadian parents of schoolchildren (65). Three papers (90)(91)(92) used the HUI3, which uses a tariff derived using a VAS and a SG technique on 504 adults from the Canadian general population (70). The mean utility scores of the five papers ranged from 0.604 - 0.74 for all stages of kidney disease prior to KT (or after failed KT), and from 0.85 - 0.99 after successful KT (80). A meta-regression revealed a significant decrease in mean HUI3 utility score of 0.138 from the baseline scenario of 0.876 for children with kidney disease before KT (80). Children with a functioning KT experienced a significant increase in HUI3 utility score of 0.111 above the baseline (80). Unfortunately, given the nature of the five studies available to Kwon *et al*, they were unable to report utilities for PD and HD specifically (80). They only reported utilities

for a homogenous group of pre-KT and failed KT patients, which may not specifically reflect those of children on one or the other form of dialysis (80).

There is little data on the quality of life of children on dialysis in Sub-Saharan Africa in general, and from South Africa in particular. In addition, as far as can be ascertained, no utility scores have been reported for African children who are on dialysis or who have had a kidney transplant. While the Pediatric Quality of Life Inventory (PedsQL 3.0) end-stage renal disease module has been used to assess the quality of life of a group of children undergoing KRT in Johannesburg (81), because the PedsQL Scales are non-preference based, the test cannot be used to directly produce health state utilities for use in HTA (112). To circumvent this issue, mapping algorithms have been developed, and validated, to allow for estimation of health state utilities from the PedsQL (112)(113)(114)(115). However, while some of these algorithms may be suitable for use where different versions of PedsQL have been used to collect health related quality of life (HRQoL) data (113), this method has not been reported with reference to the Pediatric Quality of Life Inventory (PedsQL) End Stage Renal Disease Module Version 3.0 (113).

1.3.2.2 Costs

The estimation of the costs involved in any intervention is integral to any EE (116), and accurate and reliable cost estimates form the foundation of any economic evaluation (117)(118)(119). The decision as to which costs to include in any analysis will depend on several factors, and a careful consideration of the relative importance of certain costs to the EE in question may allow the investigator to avoid wasting time on the collection of costing data that will have little or no impact on the EE's result (116). Some costs may be common to both programs under consideration and so need not be considered, some costs may be so small that excluding them will be unlikely to affect the result, and some costs, though significant, might not be needed to achieve a result that could be obtained by using a much narrower range of costs (116). In addition, it is essential to define the perspective of the EE to understand which costs need to be considered (116).

Study perspective

Studies undertaken from the health system perspective will only include the direct medical costs carried by the funder and the direct out-of-pocket costs incurred by the patient, while studies undertaken from the healthcare payer perspective will exclude patient out-of-pocket costs because they are not borne by payers (120). On the other hand, an EE undertaken from the societal perspective will include the direct medical costs carried by the funder, as well as the costs borne by the patient and society (120). These costs borne by the patient include all direct medical costs arising from out-of-pocket medical costs, and any direct non-medical costs such as those related to the need to procure food, transport, accommodation, or child-care, as a result of the illness (120).

In addition, the costs incurred by the patient may also include indirect costs such as those related to time lost from work (including time lost from school in the case of children) and the services of informal carers, and sometimes even intangible costs related to pain and suffering (116). Other costs which have been considered when using the societal perspective have also included those incurred by general society, such as the impact of the intervention on future consumption and productivity, as well as any impact on other sectors such as the criminal justice system and education sector (120).

Costs which may not be adequately reflected in market prices such as patient's leisure time, volunteer time, donated resources, and clinical space, could also be taken into account (116).

While it has been suggested that the societal perspective should be adopted for HTA assessment whenever possible (121), others suggest that this perspective may not be appropriate, or even feasible, in all cases, and that a more 'context dependent' approach be adopted when selecting the perspective of the study (122). A landmark study by the Washington Panel's publication of a Reference Case recommended that, for decision makers to be able to come to the widest possible insight into the costs and consequences of any alternative health intervention, the societal perspective be adopted (123). However, this approach is often not at all pragmatic and, although investigators will often report that the perspective they used was of the 'societal' type, practically it appears that a comprehensive investigation into the full impact that any one intervention might have on society is rarely carried out (122). In addition, while the societal burden of out-of-pocket health care costs can be significant, in lower- and middle-income

countries lack of data and technical skills in the use of EEs often results in this perspective not being adopted (124). The South African Pharmacoeconomic Evaluation Drug Pricing Committee Guidelines recommend that a third party payer (funder) perspective be adopted unless the use of a broader perspective can be justified (52).

Yang *et al* carried out a SR of EEs that specifically compared all three main forms of KRT namely PD, HD, and KT (29). Of the ten studies they identified as being suitable for inclusion in their review, only three were conducted from the societal perspective (125)(126)(127), the others being from the public healthcare perspective (128)(129)(130)(131) and the third-party payer perspective (132)(133)(134).

Once the study perspective has been decided, the sources of the costing data then need to be identified and defined (116).

Sources of data and costing methods

Once the perspective has been defined, the program inputs must be identified, their use measured, and their value quantified (119). The costing methods used in EE range from the “bottom up” micro-costing method, to the “top down” gross costing approach (135). While the micro-costing method is felt to be the most accurate (116), it may not always be the most practical or feasible of the two approaches (135).

Micro-costing involves identifying and then listing each input that will be used in the intervention, and then adding them together after allocating a unit cost value to each input (117). In addition to being very labour intensive, this method is usually unable to quantify the total health care costs (135). Gross costing involves multiplying the quantity of each service by an estimate of its unit cost, while accepting a compromise between expense and accuracy (135).

Between these two extremes lie methods such as activity-based costing (ABC), which uses automated data collection, and attempting to derive the costs of an intervention by extrapolating from cost-adjusted charges or total reimbursement (135). The disadvantage of ABC is that many hospitals do not capture this data, and that the technique may not be able to capture the

costs of new interventions (135). The disadvantages to using charges or reimbursement values to derive costs are the difficulties in obtaining costs for care received at other sites, and the potentially invalid assumption that health-care charges billed accurately reflect the economic costs of the health care delivered (135). When good administrative data is not available, the gross costing technique is likely to be the most pragmatic method to use (135).

The gross costing technique will often estimate the cost of an in-patient hospital stay by using an average daily rate (135). The problem with this approach is that it implies that all days spent in hospital will have the same cost (135). Using specialty-specific or diagnosis-weighted rates allows for the estimation of different daily costs for different areas (135).

Outpatient costs can be valued by multiplying the number of visits by a unit cost, and by comparing prescriptions to a standard set of local drug prices to obtain an estimate of the pharmacy cost (135). One caveat with this method is that the analysis of data derived from the gross costing technique will usually necessitate the use of broad analytical assumptions which, if not considered, might render the costing method insensitive to the effect of the intervention (135). In addition, broad findings derived by using the gross costing technique, based on information obtained from a single provider, may not be generalizable to other institutions (135).

While collection of the costing data as part of the study is the most accurate way to document costs, this may not always be feasible (116). In these cases, summary data from previously published clinical studies, or routinely available cost data, have been used to get cost estimates (116). In Yang *et al*'s SR, none of the studies cited obtained their own data for their analyses (29). Data from previously published papers was used by five of the ten studies (126)(127)(128)(130)(132). Other sources for cost data that Yang *et al* identified included case studies and official tariffs (133), case-mix data and medical product registries (129), hospital billing data, medical records, and patient interviews (125), health insurance system data (131), and dialysis centre annual accounts (134).

Costs of KRT

The reported costs of dialysis vary around the world. Ferguson *et al* published a CUA of dialysis in Canada (136). Their focus was on adult patients above the age of 18 years from the

providers perspective, and all costs were converted to 2016 Canadian dollars (CA\$) (136). The annual costs they used in their model were CA\$ 50 076 for in-centre HD, CA\$ 29 967 for PD, and CA\$ 39 289 for APD (136). The cost of a deceased donor KT was CA\$ 26 803, and the maintenance costs were CA\$ 13 817 for the first year after transplant and CA\$ 2 085 for subsequent years (136).

Mushi *et al* reviewed the cost of dialysis in low and middle-income countries, converting all their costs to 2012 International Dollars (Int\$) (137). In their review, the annual cost of HD ranged from Int\$ 3 424 in India to Int\$ 42 785 in Nigeria, and the annual cost of PD ranged from Int\$ 7 974 in Egypt to Int\$ 47 971 in Nigeria (137). However, the authors cautioned that, because the papers used in their review varied greatly in terms of quality, and because the resource items used in the different cost estimates varied so widely, it was almost impossible to accurately compare the cost of HD and PD from one country to another, and that it was likely that many of the reported costs were not accurate at all (137).

Mushi *et al* also reported the costs of HD in South Africa to be between Int\$ 7 370 and Int\$ 24 879, and the costs of PD between Int\$ 12 634 and Int\$ 34 178, per year (137). However, it appears that the methods used to derive these costs were the use of expert opinion (138) and a conference survey (139), rather than any real attempt at measurement of any costs incurred.

Malatji *et al* performed a retrospective analysis of dialysis costs incurred at a newly built dialysis unit at a tertiary hospital in Limpopo, South Africa (6). They used a top-down costing approach from the providers perspective, and reported their costs in 2012 United States Dollars (US\$), specifically excluding any costs associated with surgical interventions, HD and PD access creation, and hospital admissions (6). The cost data were sourced from both the hospital's pharmacy, finance, and human resources departments, as well as from annual audited expenditure statements, and it appears that all capital costs, including the actual capital cost of building the HD unit, were included in the expenditure records (6). Their cohort were all adult patients (6). They reported an average annual cost per patient for HD of US\$ 25 888, and for PD of US\$ 31 106, and the authors surmised that the additional cost of transporting PD supplies across Limpopo may have contributed to the high cost of PD when compared to HD (6). The authors noted that Karopadi *et al* (140) also found PD to be more expensive than HD in many developing countries across the world (6).

Makhele *et al* used a prospective micro-costing approach to estimate the healthcare costs of 46 adult patients receiving HD and PD at a tertiary academic hospital in Gauteng (141). They reported all costs in South African Rands (ZAR) and then converted them to 2017 US\$ (141). The perspective of the study was also that of the healthcare provider, and the costs were divided into initiation and maintenance costs, and then into fixed, semi-variable, and variable costs (141). They included all surgical costs related to the creation, and maintenance, of access for the two modes of therapy, but did not include the capital costs of the equipment or the building (141). They reported the annual cost of HD as US\$ 31 993.12 per patient and the annual cost of PD of US\$ 25 282.39 per patient (141). The costs were then further divided into the fixed costs, the semi-variable costs (including staff costs), the variable costs (HD and PD consumables), and the medication costs for both HD and PD per patient per year as follows (141): For HD, the fixed costs were US\$ 16 231.45, the semi-variable costs (including staff costs) were US\$ 7 593.71, the variable costs were US\$ 7 425.63, and the medication costs were US\$ 742.33 per patient per year (141). For PD the fixed costs were US\$ 0, the semi-variable costs (including staff costs) were US\$ 954.35, the variable costs were US\$ 20 488.79, and the medication costs were US\$ 3 839.26 per patient per year (141). Their finding that the overall annual cost of HD is more expensive than PD is in accordance with data from other first world countries (136).

Costs of KRT in children

Camargo *et al* performed a retrospective review of the costs of KRT in a cohort of 30 children who underwent HD followed by KT (142). They examined their costs from the provider's perspective using their hospital's administrative database and the national price list for medication and consumables, and they converted all their values into November 2013 US\$ (142). The mean monthly cost for conventional HD was US\$ 2 800 (SD US\$2100) and the mean monthly cost of a post-KT patient was US\$ 1 700 (SD US\$ 4 500) (142). They noted that while initially post-transplant patients incurred very high costs, their costs subsequently reduce resulting in an overall saving when compared to HD (142).

Other costs

The number of days spent in hospital has a significant effect on the cost of a hospital stay (143). Paediatric CKD has been associated with longer LOS, and also higher in-hospital costs, than

other chronic conditions, possibly due to the increased level of complexity associated with this condition (36). In addition, prolonged LOS of hospitalised children in general has also been associated with children from a low socioeconomic background, and also with children who live further from hospital (37). Although some longer admissions are associated with lower per day hospital costs due to the lower level of care required, each extra day spent in hospital will contribute to the final cost incurred for the treatment of each individual patient (143).

In South Africa, Ramjee extrapolated the estimated cost per day in hospital for 2010/2011 using an average cost for a mix of public sector facilities which included district, regional, and tertiary, hospital beds (143). In this report, the costs used to obtain the cost per day estimate were derived from data which included outpatient visits as there was no data available that split inpatient and outpatient costs for the public service (143). It also appears from the report that the cost per day was an estimate of the total costs inclusive of treatment costs, and was not just a 'bed cost' alone (143).

Ramjee estimated that the average cost for the representative mix of public sector facilities was around ZAR 2 200 per day, while the average cost per day at a private facility was around ZAR 4 300 (143). However, the report did note that the average cost per patient day varies significantly between the different levels of care provided by the different types of hospitals (143). Citing data from the Western Cape Governments Annual Performance Plan 2012/2013 (144), they highlighted that the cost per day for a tertiary hospital was around ZAR 4 200, much closer to that of the cost per day of the private facilities (143).

Other costs include lost work opportunities for caregivers (21). In South Africa, more than 50% of children with dialysis dependent CKD will need to be accompanied to the hospital by their caregivers, resulting in many caregivers being unable to find gainful employment (21). In addition, the cost of transportation to and from the hospital also makes up a significant percentage of the monthly family income (21). As explained previously, HD takes place in hospital at least three times a week while stable PD patients are treated at home, and only need to come to the hospital for monthly check-ups. This results in the families of children on HD having to spend almost five times more of their monthly family income on travel than the parents of children on PD (21).

In the case of children with ESKD being treated at NMCH, another societal cost is that incurred by MH, which plays a vital role in accommodating many of the hospital's ESKD patients who come from far away (40).

1.3.2.3 Decision analytic modelling

Once there is clarity on the health benefits and the costs of the different treatment options being compared, decision-analytical modelling allows for the definition of a set of mathematically related health pathways that will represent the range of possible disease outcomes as impacted by the interventions the health economist will be evaluating (145).

Modelling will allow for the translation of all the evidence into an estimate of the cost and consequences of the alternative options being compared, so that one can identify which option is best in terms of its costs and consequences (145). Good models should be based on the best evidence available and they should be transparent and reproducible (146). Good models should also accommodate the use of a sensitivity analysis to address uncertainties around the model structure and the data inputs (146).

All models hinge on three main factors; the time horizon, the transition probabilities, and the expected values of each possible outcome in terms of financial cost and health benefit, utility, or consequence (145). However, as opposed to decision trees which only allow progress of the patient through a model in one direction, and cannot accommodate progress of the patient over a period of time, Markov models are very appropriate for chronic diseases when assessing the path of a patient, or a group of patients, through different health states over time (147). In Yang *et al*'s SR, eight of the ten studies that met their inclusion criteria used Markov models for their evaluations (29).

In the Markov model, patients occupy a series of defined states during given points in time, and the probability of a patient occupying a given state is assessed over a period of cycles, or discreet time periods (145). Each state will have a cost and a HRQoL or utility weight associated with it, and the final expected costs and outcomes of the intervention being studied are derived by weighing the time that the patient spends in each state, by the costs and utility scores associated with that state (145).

The Markov states are selected to include all the relevant clinical scenarios, and are mutually exclusive in that a person cannot be in more than one state at a time (147). Usually only a finite, and feasibly small, set of states is defined, and people will cycle from one state to the other, except for the “Dead” state which is called an “absorbing” state (147). In Yang *et al*’s SR, while some studies used eight, 12, and even 38 states, the majority used only four states namely PD, HD, KT, and Death (29).

The cycle lengths are generally determined by the interventions being evaluated and the disease process under investigation, but are usually selected to limit the probability that a given patient will experience more than one event during the period of a cycle (145). In Yang *et al*’s SR both one month, and one year, were chosen as the cycle lengths (29).

The speed with which the patients move through the different states of the model is determined by the probability of a given patient moving from one state to another during the duration of the study period (145). The baseline transition probabilities are usually obtained from the published literature, often from longitudinal cohort studies (145). However, anecdotal evidence, expert opinion, or small non-randomised studies, while much less accurate, might also need to be used if appropriate data is not readily available (146). In Yang *et al*’s SR, the majority of the studies that reported using Markov models obtained their transition probabilities from national or international registries (29).

The choice of the time horizon, the period of time to be covered by the analysis, needs to be long enough to be able to cover all the main costs and health consequences (145). In Yang *et al*’s SR the time horizons in the studies that used Markov models ranged from five to 15 years (29).

Societies prefer to have resources available now as opposed to a later time and so, in the Markov model, future benefits and costs are discounted so that financial resources spent or saved in future years will not affect program decisions as much as those that will be spent or saved today (148). Occasionally official guidelines published by the jurisdiction concerned will recommend a discount rate but, if an official rate is not available, it is suggested that the analysis be conducted using rates used in the literature in order to facilitate comparisons with other studies (148). This rate typically ranges between three and five percent per year (116).

In Yang *et al*'s SR the discounting rates were the same for costs and consequences in each study, and ranged between three and six percent per year (29). The South African Pharmacoeconomic Evaluation Drug Pricing Committee Guidelines recommend that a discount rate of five percent per year for both costs and benefits be used, along with a sensitivity analysis measuring the impact of a discount rate ranging from zero to ten percent (52).

Although patients will be moving between Markov states in a continuous fashion, the models assume that movement between states only occurs at the beginning, or at the end, of a cycle (149). This assumption could lead the model overestimating, or underestimating, life expectancy (150). Midcycle corrections are an attempt to adjust for this by assuming that patients will, on average, switch states midway through the cycle (149). The use of the standard midcycle correction is controversial, and it may not be valid in all cases (151). In addition, in economic analysis, while the magnitude of the health and cost outcomes may be significantly affected by midcycle corrections, they are unlikely to affect incremental analyses which examine additional costs versus additional benefits, and so they may be omitted (149). None of the papers referred to in Yang *et al*'s SR that used Markov models mentioned the use of midcycle corrections in their methods (29).

Once the Markov model has been designed, the costs and utilities entered into the model, and the model has been run, an incremental analysis of the costs and consequences of the alternatives needs to be carried out (148). The ICER is a summary measure used to report on the cost effectiveness of different interventions (152).

1.3.2.4 ICER and Cost Effectiveness Thresholds

Societies in general, and funders in particular, need to ensure that choices made when deciding on which health interventions to invest in are carried out in the best possible way, so as to ensure that the best value-for-money mix of clinical and cost effectiveness is provided to the population (51)(153). Economic evaluations in the health sector involve comparing the costs and the consequences, or benefits, of alternative health interventions (51), and are usually presented as ICERs expressed as either the incremental cost per QALY gained, or the incremental cost per DALY prevented (154).

Some proposed interventions offer more health benefits, and are cheaper, than the alternatives and are considered to “dominate”, in that they are more cost effective than the alternatives (155). As logic would dictate, it would then be recommended that these take precedence over the alternatives when deciding on which intervention to use for any given program (155). Likewise, alternatives which are more expensive and offer less benefits are not cost effective, and are considered “dominated” (155). In Yang *et al*’s SR, of the studies that used Markov modelling, all but one found that KT was dominant over PD and HD, and all suggested that PD was more cost-effective than HD (29).

In many instances the new therapy, although offering more health benefits, will cost more. In these cases, the decision on whether the new intervention should be considered cost effective and approved for use, or not, depends on the value of what will be given up as a consequence, namely the opportunity cost (155). As Drummond *et al* explain, “*the real cost of any program is not the amount the program will cost the funder, but rather the value of the benefits which could have been obtained using another program which are now forgone*” (51).

Whether considering the marginal costs of health care spending (the supply side of the “market” for QALYs), or society’s willingness to pay (WTP) for a QALY (the demand side of the “market” for QALYs), any statement about cost effectiveness relies on some assessment of an appropriate threshold below which the intervention might be considered to be cost effective (155). This threshold is known as the cost effectiveness threshold (CET) (155).

CETs have been promoted for their usefulness in improving efficiency and encouraging consistency, trust, transparency, and equity, in health technology decision making (156). The criticisms of CETs are that the assumptions used in their derivation often do not apply in all circumstances (157), that CETs have led to increased health spending (158), and that CETs have encouraged companies to set their prices to come in just below the CET (159).

CETs which are set too high will result in important technologies being excluded from selection, and CETs which are set too low will result in resources being diverted away from possibly more appropriate programs (155). The methods used for CET derivation include arbitrary threshold setting such as using heuristics for threshold value estimation, the use of

explicit thresholds, and league tables (153)(160)(161). Empirical estimates used to determine CETs include demand and supply side methods (161).

A classic CET was the one initially promoted by WHO-CHOICE which used a heuristic of one to three times the gross domestic product (GDP) per capita (162). Although these estimates are now considered to be based on research that is perhaps out of date and not rigorously derived (162), these estimates have become widely adopted, especially in low- and middle-income countries (160).

There are four main limitations associated with the arbitrary use of GDP as a threshold; the technical capacity of the country's ability to roll-out the intervention is not taken into account, many non-essential health interventions might fall below the CET, the approach is based on untested assumptions, and affordability is not taken into account (160). These limitations result in CETs derived from the GDP often being too high for low and middle income countries (160). Given these limitations, the indiscriminate use of this GDP based threshold has now been discouraged (163).

A systematic review of papers studying national CET and WTP per QALY reported WTP per QALY in 2015 US\$ (164). They reported on studies from 17 countries around the world and found that the average WTP per QALY was US\$ 77 509 (US\$ 1 415 – US\$ 123 695) which, for most countries, fell within the World Health Organisation (WHO) recommendation of one to three times the GDP per capita (164). In their review only the United Kingdom, Ireland, and Thailand, used an explicit WTP (164) .

Even though CETs set by the use of explicit thresholds may have more local relevance than GDP related CETs, they also have shortcomings (160). If they are not constantly reviewed and updated they may end up not reflecting the current burden of disease, the opportunity costs of new technologies, or society's current views on their willingness to pay for certain interventions (160). In addition, they also don't take into account that there may be new options that might have better ICERs than the benchmark (160,165). Also, when using CETs, it should be noted that they are really only for interventions which will have a small impact on the budget, that the disinvestments should come from the least cost effective interventions, and that all information on the overall budget, the costs and the QALYs of all the alternatives, are assumed to be known (153).

Because arbitrarily set explicit CETs might be too high for low and middle income countries, empirical estimation has been used to set both demand and supply side CETs (153). These context specific empiric estimates of CET are likely to be more reliable than arbitrary estimations but should take affordability, and also feasibility and equity, into account (163).

To evaluate demand side CETs, WTP surveys which estimate the utility values and WTP for a health gain, and then combine the two to derive the WTP for a QALY, have been used (161). Assumptions of linearity, and the aggregation of answers from two different processes, are limitations of this method (161). Another method to determine the demand side WTP is the value of a statistical life (VSL) analysis (161). This method uses the human capital approach, reductions in mortality risk surveys, or the observation of individual market behaviour, to infer the value of a QALY (161). It's limitations include how lives are valued, and the rate at which the VSL changes with life expectancy (161).

Supply side CETs can be derived using past funding decisions, which requires complete transparency about how funding decisions were taken, and empirical marginal cost of a QALY estimation, where data limitation and endogeneity may affect results (161). Context specific empiric estimates of CET are likely to be more reliable than arbitrary estimations but should take affordability, and also feasibility and equity into account (163).

In Yang *et al*'s SR (29), while one study that used Markov modelling found that KT did not dominate HD or PD, when KT was compared to the other modes of KRT using a given WTP CET, it was more cost effective than the others (125). While no cost per QALY CET has been formally recommended for South Africa, an indirect estimation of a cost per DALY averted suggested that the threshold, for South Africa, is approximately ZAR 38 500 per DALY averted (166). This value came to around 53% of South Africa's 2015 GDP per capita, much less than the WHO-CHOICE heuristic of one to three times the gross domestic product (GDP) per capita (166).

All EEs will have a certain degree of imprecision, uncertainty, or methodological controversy attached to them (148), and an analysis of the level of uncertainty in the EE will allow for a clearer assessment of how much confidence we can place in decisions that might be taken on the basis of the EE, and can also give direction on whether the collection of additional information might better inform the decision (167).

1.3.2.5 Sensitivity analysis

Briggs *et al* state that “*the systematic examination and responsible reporting of uncertainty are hallmarks of good modelling practice*” and that “*all modelling studies should include an uncertainty assessment as it pertains to the decision problem being addressed*” (167). The methods used to deal with this uncertainty will differ depending on the source of the uncertainty and the type of EE being done (148). Briggs *et al* explain that there are four main levels at which uncertainty might arise (167):

1. Stochastic uncertainty refers to the fact that individuals, when faced with the same probabilities and outcomes, will randomly experience the effects of a disease or intervention differently.
2. Heterogeneity refers to the extent that any variability between patients might be explained by patient characteristics that could be identified by a sub-group analysis.
3. Parameter uncertainty refers to the fact that the probabilities and the other key parameters that will be used in the model are themselves uncertain because they too are only estimated quantities.
4. Structural uncertainty refers to the uncertainty around the structural assumptions made in the construction of the decision model.

Stochastic uncertainty and heterogeneity apply to patient data collected from a sample of the population as part of a study (168). Any uncertainty related to estimates based on the sample will be inversely related to the size of the sample, and therefore standard statistical methods are needed to estimate confidence intervals around these point estimates (168).

In economic evaluations, it is more usual for data to be collated from multiple sources which might include hospital records, literature reviews, and even clinical judgement (168). In these cases the significance of parameter and structural uncertainty on the outcome of the study cannot be evaluated by using standard statistical methods, and therefore sensitivity analysis is used to systematically test the influence of the variables and assumptions used in the evaluation on the outcome (168).

There are three main types of sensitivity analysis (169). In a deterministic sensitivity analysis (DSA), the effect of adjusting one or more of the parameters, across a plausible range, on the

cost, the effects, or the ICER, is determined (169). The results are then usually depicted using line graphs or tornado diagrams (169). In extreme scenario analysis, a multi-way analysis is performed using “best case” and “worse case” scenarios (169). These methods are useful in ascertaining the ‘threshold’ values that the parameters would need to have in order to enable a decision on which intervention is more cost effective to be taken (170). However, one problem with these types of sensitivity analyses is that they do not address the relative likelihood that the values or scenarios being evaluated will occur (169).

Probabilistic sensitivity analysis (PSA) attempts to overcome this challenge by using computer-based Monte Carlo simulations in which distributions are assigned to each of the model parameters, and then randomly sampled and fed through the model multiple times to generate a large group of single estimates of cost and benefits (170). In this way, the range of values that the parameters are likely to take is depicted by the range of outputs, thus providing the analyst with a more correct estimate of the net benefits, and also the proportion of time (the probability) that each alternative will be cost effective (170). The choice of the use of a particular distribution is informed by the nature of the parameter itself, as well as by the way the parameter was estimated, and the summary statistics are reported (170).

The results of all three methods can be depicted on a cost-effectiveness plane with the horizontal axis representing the difference in effect between the conventional treatment and the new technology, and the vertical axis showing the difference in cost (169). Cost-effectiveness acceptability curves (CEACs), drawn by transforming each set of costs and benefits for each alternative into expected net benefit, and then plotting the probability that it will have the highest net benefit using a cost effectiveness threshold, are also used to demonstrate the cost effectiveness of different options (170).

In Yang *et al*’s systematic review, while all the studies reviewed performed sensitivity analyses on their parameters, none addressed uncertainty related to the structure of their models (29). Of the studies that used Markov Modelling, one study used PSA alone (129), two used a combination of DSA and PSA (125)(133), and the rest used DSA alone (29).

1.4 NMCH as the site of the study

Historically, in South Africa, the Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, the Steve Biko Academic Hospital (SBAH), Pretoria, the Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, the Dr George Mukhari Academic Hospital (DGMAH), Ga-Rankuwa, the Universitas Academic Hospital (UAH), Bloemfontein, and the Charlotte Maxeke Academic Hospital (CMJAH) in Johannesburg, all offered paediatric ESKD programs (171). However, only the RCWMCH, IALCH, and CMJAH, offered large and comprehensive paediatric dialysis and transplant services (13)(14)(172)(173).

In 2005 the former President of South Africa, Mr Nelson Mandela, expressed his wish for better medical care for the children of the region (174). To achieve this goal the Nelson Mandela Children's Hospital Trust was established in 2009 and, by December 2016, the Nelson Mandela Children's Hospital was built (174). The hospital was then opened in phases, with the dialysis unit admitting its first patients in March 2018 (7).

Unpublished data from NMCH, combined with data derived from personal communication with the Divisional Heads of Paediatric Nephrology at all academic centres offering tertiary paediatric nephrology services across the country, show that, since its inception in 2018, the dialysis unit at NMCH has grown to become the largest paediatric dialysis service nationwide.

The data show that NMCH currently services around 30% of all children on dialysis in the whole of South Africa and, of the children cared for by the public health sector, NMCH services around 40% of all children on chronic KRT, 30% of all children on PD, and 60% of all children on HD nationwide. For patients coming from Gauteng, Limpopo, North-West, and Mpumalanga, the unit services 55% of all children on dialysis, 30% of all children on PD, and 80% of all children on HD.

These numbers make it very likely that the patient demographic, disease profile, and clinical journey, seen at NMCH is very representative of the patient demographic, disease profile, and clinical journey, of all children being treated for ESKD in the public health sector countrywide.

To our knowledge, no DSA or PSA has been performed on a cohort of children with ESKD in South Africa up until this point. Therefore, this study was initiated to inform the planning of tertiary paediatric dialysis programs nationwide in general, and for PH in particular.

CHAPTER TWO

METHODS

This chapter provides details of the methodology used in this study. Details on the study design, study population, data collection, and analysis, are presented.

2.1 Study Design

The method was designed to conform to the recommendations of the CHEERS 2022 checklist (54). A plagiarism declaration was signed by the candidate (Appendix 1).

The study was entirely self-funded. The principal investigator grew up in Polokwane and is the Head of Paediatric Nephrology at NMCH. There are no other conflicts of interest. The Markov model was designed by the principal investigator and is not publicly available elsewhere.

A CUA was performed using decision analytical modelling. The CUA was conducted using expected costs and benefits generated by a Markov model built using Excel 16.0® and using a cycle length of one year. The analytical model was structured around a hypothetical study population of children, aged from birth to 16 years of age, who were not on a medical aid, who were resident in the referral/drainage area of PH, and who needed KRT for the treatment of their ESKD.

The effectiveness measure or health outcome used was the QALY. The cost effectiveness was evaluated by analysing incremental cost effectiveness ratios (ICER) and incremental net monetary benefits generated by the analysis.

All cost data was obtained from a cohort of 55 children receiving chronic kidney replacement therapy (dialysis and/or kidney transplant) at the Nelson Mandela Children's Hospital (NMCH) between 1 April 2019 and 31 March 2022. Thirty-three of the children come from closer than 150 km to NMCH, and 22 came from further than 150 km from NMCH.

Establishing a satellite chronic CRT service at PH would allow children who live closer than 150km to PH to receive their care, under the guidance of the unit at NMCH, at PH rather than at NMCH as is currently the case.

This dissertation examines the estimated costs and benefits of the hypothetical establishment of a satellite dialysis unit for children with ESKD at PH. The model proposes that children from PH with ESKD in need of kidney replacement therapy (KRT) would be referred to NMCH for evaluation. Those deemed fit for treatment would be initiated on dialysis at NMCH and listed for kidney transplantation on the NMCH kidney transplant (KT) list. Once stable on dialysis, they would then be transitioned back to the hypothetical satellite unit at PH for follow up and treatment, and to await their transplant call up. Patients called up for a KT would have their transplant at NMCH and then, once stable, would also be referred to PH for long-term follow up under the direction of the team at NMCH.

The comparator was the current situation, in which paediatric patients referred to PH with ESKD in need of dialysis therapy are referred to tertiary hospitals in Pretoria or Johannesburg for evaluation and, if deemed suitable, for long term treatment based at those hospitals. NMCH was assumed to be the tertiary hospital for the purposes of the model. These children must travel more than 150 km to receive care at NMCH. ***This group was represented by data from children treated at NMCH with HD or PD and whose home address was more than 150 km from NMCH, and by a group of “Unstable KT” patients.***

The intervention was the theoretical establishment of a satellite paediatric dialysis unit at PH that would be able to care for children already established on chronic KRT by NMCH. The model analysed the costs incurred and the QALYs gained if the paediatric patients referred to PH with ESKD in need of dialysis therapy that had then been referred to, evaluated by, accepted onto, and then established on, the long-term KRT program at NMCH, would then be sent back to PH for their long term KRT until they received a KT. Once transplanted successfully, they would be sent back to PH for long term follow up under the guidance of the team at NMCH. These children will have to travel less than 150 km to seek care, in this case at the satellite unit at PH. ***This group was represented by data from children treated at NMCH with HD or PD whose home address was less than 150 km from NMCH, and by a group of “Stable KT” patients.***

For KT patients, because PH is regarded as a satellite unit and would only be caring for stable KT patients, the KT group was divided into two groups; a '*Stable KT*' group represented by children with a KT who did not need to go back onto dialysis during the data capture period, and an '*Unstable KT*' group represented by children who did need to go back onto dialysis during the data capture period. The cost and LOS data from the Stable KT group were used for the KT data for the intervention, while the cost and LOS data from the Unstable KT group were used for the KT data for the comparator.

We are comparing the costs and benefits of the comparator to the costs and benefits of the intervention.

To enable the capturing of all the main costs and health consequences of a child transitioning through the system to adulthood, the CUA was conducted from the perspectives of both the "healthcare payer" (The Limpopo Department of Health and the executive management of PH), as well as the "societal" perspectives.

Due the shortage of adult dialysis unit slots, patients treated in the public service paediatric dialysis units in South Africa will commonly transition to the adult services only in their late teenage years, and in some cases in their early twenties. To ensure that all these costs and consequences were taken into account, the analytical time horizon for the study was set at twenty years.

As recommended by the South African Pharmacoeconomic Evaluation Drug Pricing Committee Guidelines, a discount rate of five percent per year for both costs and benefits was used (52).

An ingredients-based approach to the costing was used, and a purposive sampling process was used to select the sources for the other model parameters (Table 2.1).

All costs were converted to, and reported in, 2022 ZAR using an inflation rate of 7% (175) and the Compound Interest Formula (176) as follows:

Value in ZAR (2022) = Reported Cost × (1 + Inflation Rate) ^ (2022 - Year of Reported Cost)

Once permission had been granted by the NMCH management, and ethical clearance had been obtained from the Wits Human Research Ethics Committee (HREC) for the study to proceed (Appendix 2), the records of the Division of Paediatric Nephrology at NMCH were used to compile a list of all children who had been referred to, and treated by, NMCH for ESKD. The caregivers of these patients were then contacted, and informed consent was obtained for collection of their child's data for the purposes of the study. Informed assent for data collection was also obtained from those children who were able to provide such assent. In addition, direct communication via telephone and email was instituted with the heads of paediatric nephrology at the other academic hospitals around the country, as well as the Head of the Department of Paediatrics and Child Health at PH, regarding their role in the data collection.

Four months of treatment was selected as the minimum duration of treatment to fit in with the definition of chronic ESKD (10). All data of children whose parents/guardians gave consent to the study, and who were treated for ESKD for at least four months at NMCH on any of the three modes (PD, HD, KT), were included in the study.

All data of children whose parents/guardians refused consent to the study, or who were treated for ESKD for less than four months at NMCH on any of the three modes, or were incomplete, were excluded from the study.

Establishing a satellite chronic CRT service at PH would allow children who live closer than 150km to PH to receive their care, under the guidance of the unit at NMCH, at PH rather than at NMCH as is currently the case. PH is situated 312 km from NMCH (177), and so the data set was divided into two groups for the cost and length of stay analysis using distance from the patient's home address to NMCH; one group from further than 150 km away (representing the comparator), and a second group from closer than 150 km away (representing the intervention).

2.1.1 Identification of data sources

2.1.1.1 Method for the literature review

- **Population:** all studies reporting on paediatric ESKD patients.
- **Intervention:** all studies reporting on children with ESKD on chronic dialysis, or who had a KT.
- **Study designs:** the study designs included were meta-analyses, longitudinal cohort studies, cross sectional prevalence studies, single centre reports, conference abstracts, and registry reports.
- **Measurement of outcomes:** studies which reported on outcome, mortality, survival, complications, readmission rates, transplant rates, and quality of life and utility scores were included.
- **Search strategy:** the search strategy took the following form: (terms for ESKD, paediatrics, dialysis, and transplantation) AND (a bespoke methodological search filter to locate studies which report on outcome, mortality, complications, readmission rates, transplantation rates, and quality of life and utility scores). The search strategy was informed by the Centre for Reviews and Dissemination guidelines (178). It was guided by librarians at the Wits Health Sciences Library and was run in the following databases: Pubmed, Econlit (via EBSCO Host), Web of Science (via ISI), Medline (via EBSCO Host), and on Google Scholar.
- **The search limit:** only papers or abstracts published in the English language literature between January 2009 and July 2023 were selected.
- **Search recording and reference manager:** Zotero (179)
- **Study selection:** screening and article selection was performed by the principal investigator.
- **Data extraction:** a data extraction form was used which collected the following details.
 - The type of study
 - The setting of the study
 - The population
 - The outcome variables
- **Data synthesis:** the variables were tabulated and summarised.

2.2 Markov Model

2.2.1 Markov States

For the Markov model, the patients were assumed to move through six Markov states as depicted in Figure 2.1 below. ***State F, death, is the only absorbing state in the model.***

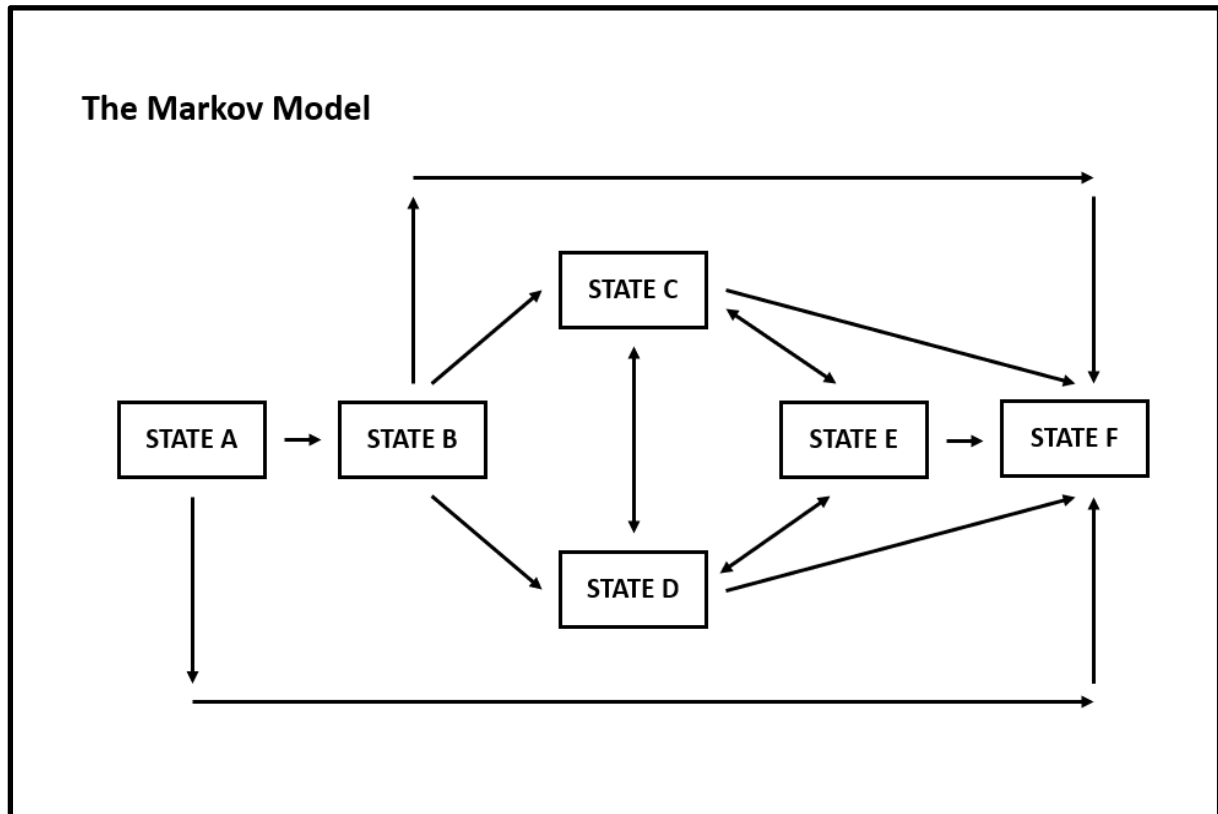
These states were selected based on our own clinical experience, as well as on those used by similar studies in the literature (29).

State A reflects ***the probability of a new patient presenting with undiagnosed ESKD to PH being deemed suitable for referral on to NMCH for further evaluation*** after the diagnosis has been established by PH. As such, only unidirectional flow is permitted for State A with only two possible outcomes; the patients are either referred onto NMCH and move into State B, or they are deemed unsuitable for referral for various reasons and they die from their condition, moving into State F.

State B reflects ***the probability of the children referred from PH being deemed suitable for long term management of their condition at NMCH.*** Once a child has been accepted onto the program, the mode of therapy, viz peritoneal dialysis vs haemodialysis, is decided upon by the treating team at NMCH. No patients at NMCH are taken off the program once accepted, and the model assumes that no patients would arrive in State B stable enough to allow for conservative management off dialysis while they undergo evaluation for a pre-emptive KT. As such, only unidirectional flow is permitted for State B with three possible outcomes; either they are accepted for the program and are placed onto PD (moving into State C) or onto HD (moving into State D) or, for various reasons, they are deemed unsuitable for the program and they will die, moving into State F.

States C, D, and E represent ***the probabilities of movement between States C, D, and E, as well as into State F, from States C, D, and E.*** Patients in States C and D are automatically worked up and listed for a KT. Due to the nature of KRT, there is bidirectional movement between States C, D, and E. In addition, there is a mortality rate associated with each of these three states and so, there will also be movement from States C, D, and E, into State F, death.

Figure 2.1 The Markov Model



State A: *Newly diagnosed ESKD presenting to PH, but not yet referred on to NMCH for evaluation.*

State B: *Newly diagnosed ESKD presenting to PH, referred on to NMCH for evaluation, but not yet accepted onto a KRT program.*

State C: *ESKD established on Peritoneal Dialysis (PD)*

State D: *ESKD established on Haemodialysis (HD)*

State E: *ESKD stable with a functional Kidney Transplant (KT)*

State F: *Death*

2.2.2 Transition probabilities

The transition probabilities for States A and B were derived from data obtained from NMCH, as well as from the Head of the Department of Paediatrics at PH, and from the heads of the seven academic paediatric nephrology divisions around the country, viz the RCWMCH, IALCH, SBAH, CHBAH, DGMAH, UAH, and CMJAH.

These units are the only ones which provide a comprehensive paediatric CKD program in South Africa. As such, the data obtained from them were assumed to be representative of the study population transition rates in question for the purposes of the model.

An introductory telephone call was made to each of the respondents to explain, and to discuss, the study, and a follow up email requesting participation was also sent. Additional ethics approval was requested by, and obtained from, the University of KZN (Appendix 3) and the Department of Health in Limpopo (Appendix 4).

A bespoke data capture questionnaire (Table 2.1) was then emailed to the Heads of Paediatric Nephrology listed above, and to the Head of Paediatrics at PH. Information on the number of patients referred annually, the number patients rejected per year, and the number of patients rejected per year due to distance alone amongst other information, was captured to allow us to estimate transition rates for the study.

After this was completed and submitted, a follow up telephone call was made to each of the respondents by the principal investigator to confirm, and to discuss, the results.

Table 2.1 Questionnaire sent to the academic heads and HOD Dept Paediatrics, Polokwane Hospital

Hospital	Please suffix with an 'E' if estimated	Please suffix with an 'E' if estimated
	Average	Range
General		
Number of new referrals per year		
Number rejected per year		
Number rejected per year - distance alone		
Transplant		
Number of transplants per year		
Number of TP at any one time		
Graft failure per year		
Back to PD per year		
Back to HD per year		
TP deaths per year		
TP admissions per year per px- ward		
TP duration of stay per px- ward		
TP admissions per year per px ICU		
TP duration of stay per px- ICU		
HD		
Number on HD at any one time		
Switch to PD per year		
HD deaths per year		
HD admissions per year per px- ward		
HD duration of stay per px- ward in days		
HD admissions per year per px ICU		
HD duration of stay per px- ICU in days		
PD		
Number on PD at any one time		
Switch to HD per year		
PD deaths per year		
PD admissions per year per px- ward		
PD duration of stay - ward in days		
PD admissions per year per px - ICU		
PD duration of stay - ICU days		

State A

The respondents listed above were asked to provide a mean and range of the total (or an estimated total if the data was not available) number of new ESKD patients that present to their facilities per year. These numbers were then captured onto an Excel spreadsheet and collated to give a mean and range of the expected total number of new ESKD patients per year ***for entry into State A of the model for both the comparator and the intervention.***

The respondents were also asked to provide a mean and range of the total (or estimated total if the data was not available) number of new ESKD patients who might be rejected from entry into the referral hospitals' ESKD program due to distance from hospital alone (i.e., those deemed to live too far away from a tertiary centre to be able to access care timeously and regularly).

These numbers were then also captured onto an Excel spreadsheet and collated to give a mean and range of the expected total number of new ESKD patients per year who might be rejected from the comparator's ESKD program due to distance from hospital alone.

This number was then divided by the average number of expected new ESKD patients per year to give the probability of a child being denied entry into the program due to distance alone, thereby ultimately dying, and ***moving from State A to State F of the model for the comparator.*** This number was also used along with the total number of new patients entering State A per year, as the alpha and beta values respectively, for this variable's part of the PSA.

The difference between the expected total number of new ESKD patients per year who might be rejected from the comparator's ESKD program due to distance from hospital alone and the average number of expected new ESKD patients per year was then divided by the expected number of new ESKD patients per year to give the probability of a child being admitted into the comparators ESKD program as represented by ***movement from State A to State B for the comparator.*** This number was also used along with the total number of new patients entering State A per year, as the alpha and beta values respectively, for this variable's part of the PSA.

Because the intervention specifically looked at making the ESKD service accessible to patients from far away, it was assumed that, ***for the intervention, no patients entering State A would be rejected due to distance alone, and all would progress to State B immediately.***

Only unidirectional movement was allowed from State A to State B.

State B

For the probabilities associated with State B, the respondents from the tertiary centres were asked to provide a mean and range of the total (or estimated total if the data was not available) number of new ESKD patients who might be rejected from entry into the referral hospitals' ESKD program due a medical or social reason, excluding distance from hospital.

These numbers were captured onto an Excel spreadsheet and collated to give a mean and range of the expected total number of new ESKD patients per year who might be rejected from both the comparator and the intervention's ESKD program due to a medical or social reason, excluding distance from hospital.

This number was then divided by the average number of expected new ESKD patients entering State B from State A per year to give the probability of a child being denied entry into the program due to a medical or social reason, excluding distance from hospital, thereby ultimately dying, and ***moving from State B to State F of the model for both the comparator and the intervention.*** This number was also used along with the total number of new patients entering State B per year, as the alpha and beta values respectively, for this variable's part of the PSA.

The transition probabilities for the movement from State B to State C, and from State B to State D, were determined from data obtained from NMCH for patients treated between the 1 April 2019 and the 31 March 2022. The transition probabilities were calculated from retrospective data obtained from the patient hard copy files securely stored in the Division of Paediatric Nephrology at NMCH, and the Fresenius Medical Care Therapy Monitor (TMON V2.3) (180) and Therapy Support Suite (TSS) (181) electronic medical record systems used by the unit. Only data from children who had been on a mode for at least four months were included in the analysis.

For new referrals, the decision whether to start PD or HD for their KRT is often dependent on how far they live from NMCH. For this reason, the probabilities of moving from State B to State C and from State B to State D were determined separately for the group of children who

came from closer than 150 km to NMCH (the Intervention), and for the group who came from further than 150 km from NMCH (the comparator).

The difference between the average number of expected new ESKD patients entering State B per year and the number of patients moving from State B to State F per year was then divided by the expected number of new ESKD patients entering State B per year and multiplied by the probability of a new patient being assigned PD thus moving from **State B to State C**, or by the probability of a new patient being assigned HD thus moving from **State B to State D**. This was done for both the intervention and the comparator.

These calculations gave the probability of a child being enrolled into the comparator, and the intervention's, ESKD programs as represented by ***movement from State B to State C, or from State B to State D, for the comparator and the intervention***. These numbers were also used along with the total number of new patients entering State B per year, as the alpha and beta values respectively, for these variable's part of the PSA.

It was assumed that no children would arrive early enough in their illness to be able to successfully wait for, and receive, a pre-emptive KT and move from State B to State E. Also, from this data, no child was taken off the program once enrolled, and so only unidirectional movement was allowed from State B to State C, and from State B to State D.

States C, D, and E

For States C, D, and E, and for movement from each of these states into State F, the transition probabilities were also determined from data obtained from NMCH for patients treated between the 1 April 2019 and the 31 March 2022. The transition probabilities were calculated from retrospective data obtained from the patient hard copy files securely stored in the Division of Paediatric Nephrology at NMCH, and the Fresenius Medical Care Therapy Monitor (TMON V2.3) (180) and Therapy Support Suite (TSS) (181) electronic medical record systems used by the unit. Only data from children who had been on a mode for at least four months were included in the analysis.

As these patients were now well established on KRT and already being treated by NMCH it was assumed that the transition probabilities for States C, D, and E, would be the same for both

the comparator and for the intervention. Therefore, they were derived from an analysis of the whole cohort together. Because the natural history of ESKD is that children will move from one mode of KRT to another depending on their clinical need, the transitional probabilities for bidirectional movement between States C, D, and E, were calculated.

2.2.3 Cost and LOS data

Data on cost, LOS, health effects, and other parameters, were collected from retrospective data obtained from the patient hard copy files securely stored in the Division of Paediatric Nephrology at NMCH, and the Fresenius Medical Care Therapy Monitor (TMON V2.3) (180) and Therapy Support Suite (TSS) (181) electronic medical record systems used by the unit.

All the data were collected by the principal investigator and collated onto a bespoke Excel 16.0® spreadsheet designed by the principal investigator. Other parameters were sourced from the literature (Table 2.2).

2.2.3.1 Cost data

Only data from children who had been on a mode for at least four months were included in the analysis as explained above. Data were collected on the pharmacy costs, the laboratory costs, and the blood products costs, for each patient as elaborated on below. All costing data were reported in 2022 South African Rands (ZAR).

The cost data for the pharmacy costs (PC), i.e., the total medication and dialysis consumables cost, for each patient in States C, D, and E, were obtained using the NMCH electronic pharmacy billing system, and were confirmed as correct by the head of the pharmacy at NMCH.

The cost data for the laboratory services for each patient in States C, D, and E, were obtained from the electronic versions of the monthly invoices sent to NMCH by the National Health Laboratory Services (NHLS), the sole providers of laboratory services to NMCH, and were confirmed as correct by the financial manager at NMCH.

The cost data for the blood products used by each patient in States C, D, and E, were obtained from the electronic versions of the monthly invoices sent to NMCH by the South African Blood Transfusion Services (SANBS), the sole providers of blood products to NMCH, and were also confirmed as correct by the financial manager at NMCH.

The expected PC, NHLS, and SANBS cost per patient per year on mode, was defined as the costs captured for each patient, divided by the number of months the child was on that mode, multiplied by 12, to produce a predicted yearly cost per patient for the purposes of the model.

The expected total cost per patient per year on a particular mode was defined as the sum of the PC, NHLS, and SANBS costs per patient per year spent on that mode.

Where a complete set of costing data for a particular patient was not available, that patient's data were excluded from this part of the analysis.

2.2.3.2 Length of stay data

The length of stay (LOS) data for State A were derived from an estimation of the mean LOS for a new CKD 5 patient at PH as reported by the Head of the Department of Paediatrics at PH.

The LOS for States B, C, D, and E, were derived from the patient hard copy files securely stored in the Division of Paediatric Nephrology at NMCH, the Fresenius Medical Care Therapy Monitor (TMON V2.3) (180) and Therapy Support Suite (TSS) (181) systems used by the unit, and the hospital electronic admission and discharge database.

The patient data collection covered the period between the 1 April 2019 and the 31 March 2022 inclusively.

The patient numbers and demographic data were confirmed as correct by the nursing head in charge of the dialysis unit at NMCH, and by the other paediatric nephrologists working in the unit.

The LOS at MH for States C, D, and E for the children admitted to MH during the data capture period were obtained from the manager of MH at the time. The LOS at MH was used only in the calculations of the costs and not of the QALYs.

2.2.4 Data sources for other variables used in the model

2.2.4.1 Costs to the health system

PH already has the infrastructure of an adult dialysis unit in place (6). The model assumed that, as happens in the majority of cases worldwide (35), children needing HD at PH would be allowed access to this adult unit for KRT should they need it. For this reason, costs related to the building, and equipping, of a brand-new dialysis unit for children needing KRT at PH were not taken into account in the model.

The cost per day in hospital was taken from Ramjee as the average cost for a representative mix of public sector facilities of around ZAR 2 200 per day in 2011 (143), and then converted to 2022 ZAR.

The 2022 salary scales for a Grade One Specialist were obtained from the Limpopo Department of Health website (182).

The fixed cost and semi-variable cost of running a HD unit were obtained from Makhele *et al* (141). The fixed cost was captured, as reported, in 2017 ZAR, and then converted to 2022 ZAR. The semi variable cost was captured, as reported, in 2017 USD, then converted to 2017 ZAR using an exchange rate of 13.0738 (141), and then converted to 2022 ZAR.

Within the model the cost of the dialysis unit was calculated by dividing the predicted number of patients treated in the unit by the cost of treating the 46 patients reported by Makhele *et al* (141), and then multiplying the quotient by the cost of running the unit as reported by Makhele *et al* (141), in order to get an estimated cost per number of patients treated in the unit.

For completeness sake the salary scales for a registered nurse and for a medical officer from the Limpopo Department of Health website were also captured and recorded (182). However,

email communication with the authors of Makhele *et al* confirmed that the semi-variable costs reported by Makhele *et al* included some staff costs (nursing assistant, dialysis nurse, registrar/paediatric specialist trainee/resident, nurse, social worker, phlebotomist, anaesthesiologist, and dieticians) as reported in their paper (141), but **excluded** those of a nephrologist/consultant (Appendix 5 and Appendix 6).

Because the cost of a nephrologist was not included in the staff costs provided by Makhele *et al* (141), provision was made in the model to include this cost in the analysis. A paediatrician currently employed at PH has been earmarked to oversee the management of paediatric nephrology at PH. To take into the account the opportunity cost of the time that this person will spend caring for children needing KRT at PH, the consultant nephrologist cost was evaluated using a full-time equivalent (FTE) of 0.125 (one hour of an eight-hour workday) as recommended by the authors of Makhele *et al* (Appendix 6).

2.2.4.2 Societal costs

The cost of transport to the family for the various modes of KRT were obtained from Bello *et al* (21). The costs were captured, as reported, in 2015 ZAR and converted to 2022 ZAR.

The monthly cost (ZAR) of a stay at Marang House for 2022 was obtained from the manager of the Marang House (Appendix 7). Within the model, this cost was multiplied by the LOS at MH for State C, D, and E, and by the probability of a child in State C, D, and E being admitted to MH. This cost, along with the cost of travel to and from the hospital, was added to the other costs in the model to estimate the societal cost of the intervention.

2.2.4.3 Utilities

The utility scores for the different health states were obtained from data published by Wyld (96) and Quan (80).

2.2.4.4 Other variables

A classic CET is one initially promoted by WHO-CHOICE which uses a heuristic of one to three times the GDP per capita (162). The GDP per capita for South Africa for 2021 and 2022

ranged between US\$ 6 700 and US\$ 7 000 (183). Based on these two values, the WTP threshold for the model was set at one times the average GDP per capita for South Africa in 2022 (US\$ 6850), converted to 2022 ZAR, viz ZAR 112 000 per QALY (176). The sources for these costs, the inflation rate, the number of new cases of CKD per year, the number of new specialists needed, and the number of days taken to work up a new CKD patient at PH and at NMCH, are depicted in Table 2.2.

Table 2.2 The mean cost per person, and the data sources, for the other variables used in the model (all costs are in 2022 ZAR, and are all annual costs unless otherwise indicated)

Description 1	Mean	SE	distribution	alpha	beta	Data source
<u>Costs to the health system:</u>						
Cost per day in hospital	4 709	240	<i>gamma</i>	384	12	Ramjee (143)
Nephrologist (G1)	1 266 305	64 607	<i>gamma</i>	384	3 296	Limpopo DOH (182)
Registered Nurse	294 131	15 007	<i>gamma</i>	384	766	Limpopo DOH (182)
Medical officer	940 198	47 969	<i>gamma</i>	384	2 447	Limpopo DOH (182)
Semi-variable costs HD unit	139 243	7 104	<i>gamma</i>	384	362	Makhele (141)
Fixed costs HD unit	297 631	15 185	<i>gamma</i>	384	774	Makhele (141)
<u>Societal costs:</u>						
Travel PD	2 794	143	<i>gamma</i>	384	7	Bello (21)
Travel HD	15 377	785	<i>gamma</i>	384	40	Bello (21)
Travel TP	2 794	143	<i>gamma</i>	384	7	Bello (21)
MH cost per child per month	11 125	568	<i>gamma</i>	384	29	Marang House
<u>Utilities:</u>						
State A	0.62	0.10	<i>Beta</i>	14	9	Wyld (96)
State B	0.62	0.10	<i>Beta</i>	14	9	Wyld (96)
State C	0.74	0.06	<i>Beta</i>	40	14	Kwon (80)
State D	0.74	0.06	<i>Beta</i>	40	14	Kwon (80)
State E	0.99	0.05	<i>Beta</i>	5	0	Kwon (80)
<u>Other variables:</u>						
WTP for a QALY	112 000	-	-	-	-	Robinson (162)
Discount factor costs	0.05	-	-	-	-	ISPOR (52)
Discount factor QALYs	0.05	-	-	-	-	ISPOR (52)
Inflation rate	0.07	-	-	-	-	Stats SA (175)
New CKD cases per year	6.37	1.49	<i>gamma</i>	18	0	Primary data
No. of consultants per unit	1	0.26	<i>gamma</i>	15.37	0.07	Primary data
Work up days at PH	8	1.02	<i>gamma</i>	61	0	Primary data
Work up days at NMCH	5	1.02	<i>gamma</i>	24	0	Primary data

2.3 Statistical Analysis

The statistical analysis was performed using statistical tools and resources provided by the website Social Science Statistics (184).

Categorical variables were described using frequencies, percentages, and were compared using *Chi-squared* testing for variables containing more than five groups, and *Fisher's exact* testing for variables containing five or less groups (185).

Continuous variables were described using means, standard deviation (SD), standard error (SE), and confidence intervals (CI), as appropriate. The continuous variables were then tested for skewness. Normally distributed data was compared using the *two-sample t test*, and skewed data was compared using the *Mann-Whitney U test* (186).

The significance level for all statistical tests was set at $p < .05$.

2.4 Parameter Distributions

2.4.1 Transition probabilities and utility scores

A *beta* distribution was used, as recommended, for the transition probabilities and for the utility scores (187). The effect of the discount factor for costs and QALYs and the inflation rate were not included in the PSA.

The *alpha* values for the probabilities used in the model were calculated using the mean proportion of patients who moved between each state, or stayed in a state, over the three-year study period multiplied by the mean number of patients on that mode over the three-year study period.

The *beta* values for the probabilities used in the model were calculated by working out the difference between the alpha value and the mean number of patients on that mode over the three-year study period.

The probability was calculated by dividing the *alpha* value by the mean number of patients on that mode over the three-year study period.

The standard error (SE) for the transition probabilities was calculated from the *alpha* and *beta* values of each variable using the following formula (188):

$$SE = \sqrt{(\alpha \times \beta / ((\alpha + \beta)^2 \times (\alpha + \beta + 1)))}$$

The *alpha* values for the utilities were derived from the mean and SEs reported using the following formula (188):

$$\text{Alpha value} = \text{mean} \times (\text{mean} \times (1 - \text{mean}) / (SE^2) - 1)$$

The *beta* values for the utilities were derived from the mean and alpha values using the following formula (188):

$$\text{Beta value} = \text{Alpha value} \times (1 - \text{Mean}) / \text{Mean}$$

2.4.2 Cost and LOS

A *gamma* distribution was used, as recommended, for the cost and length of stay data (187).

The sampling distribution of the mean was used for the cost and LOS data as per Briggs *et al* (187). Standard deviations (SD) were obtained from the primary costing data and from the literature for some of the variables in the model. These were converted to the SE for the purposes of the model using the following formula (189):

$$SE = SD / \sqrt{(\text{sample size})}$$

Where a study reported only the 95% confidence intervals, the SE was obtained using the following formula (190):

$$SE = (\text{upper limit} - \text{lower limit}) / 3.92$$

Where only a mean value was reported from a data source, the minimum and maximum values were assumed to deviate by 10% from the mean (191), and were converted to the SE by adapting the preceding formula as follows (188):

$$SE = ((mean + 0.1 \times mean) - (mean - 0.1 \times mean)) / 3.92$$

The *alpha* values for the costs and LOS used in the model were derived from the mean and the SE for each parameter using the following formula (188):

$$Alpha\ value = (mean / SE)^2$$

The *beta* values for the costs and LOS used in the model were derived from the mean and the SE for each parameter using the following formula (188):

$$Beta\ value = SE^2 / mean$$

2.5 VBA macro

A Visual Basic Application (VBA) macro was used to generate 1000 Monte Carlo simulations / iterations of the model, using random sampling of each variable for each iteration according to their respective distributions, and to draw the CEAC curves (Appendix 8).

All the costs and QALYs depicted in the Results section are those generated by the Excel spreadsheet and the VBA macro, rounded off to zero decimal places.

2.6 Sensitivity analysis

Uncertainty in the model parameters was characterized using a PSA. The cost and effectiveness parameters were varied using gamma distributions for the cost parameters and beta distributions for the effectiveness parameters. A CEAC was produced for to establish the probability that a given intervention was cost-effective. The CEAC, derived from the joint distribution of the effects and costs of the intervention summarized the uncertainty in estimates of cost-effectiveness.

The results of the ICERs, as defined by the differences in cost / difference in effectiveness according to the formula $ICER = \Delta C / \Delta E$, were depicted on cost-effectiveness planes with the horizontal axis representing the difference in effectiveness between the comparator and the intervention, and the vertical axis showing the difference in cost for each iteration of the model (190).

CEACs were then created by transforming each set of costs and benefits for the comparator and the intervention into an expected net monetary benefit, and then plotting the probability that there would be a positive net monetary benefit for a range of CETs according to the following formula describing the relationship between the net monetary benefit (NMB), the value of the threshold ratio (λ), the effect difference (ΔE), and the cost difference (ΔC) (190):

$$NMB = \lambda \Delta E - \Delta C > 0$$

2.7 CHEERS checklist and Turn-it-in report

Once the study was completed, an interactive CHEERS 2022 checklist was completed (54), and a PDF report was generated (Appendix 9). In addition, a similarity Turn-it-in report was completed (Appendix 10).

CHAPTER THREE

RESULTS

This chapter describes the results of the study. It provides the results relating to the demographic details of the cohort, the costs, the benefits, and the DSA and PSA analyses.

3.1 Demographic details

A total of 62 patients were identified as receiving KRT for ESKD during the data capture period. Of these, seven received treatment for less than four months and were excluded from the analysis.

Of the remaining 55 patients 55% were male. Black South African children made up 87% of the cohort (Table 3.1). The mean age of the group at entry into the study was 10.57 years (3.08 - 17.42 years). The mean time in the study was 26 months (6 - 36 months).

The most common primary diagnosis was CAKUT (Table 3.1) which included ten children with posterior urethral valves. This was followed by steroid resistant nephrotic syndrome (Table 3.1), of which nine patients had a kidney biopsy finding of FSGS.

The mean distance of the whole group from home to NMCH was 149 km (3 - 516 km), with 33 (60%) of the children coming from closer than 150 km to NMCH and 22 (40%) coming from further than 150 km from NMCH.

Twenty-one patients were on PD for at least four months, with a mean duration of being on PD during the study period of 15 months (5 – 36 months). Of these, 48% came from closer than 150 km to NMCH (Table 3.2).

Thirty-nine patients were on HD for at least four months, with a mean duration of being on HD during the study period of 18 months (4 – 36 months). Of these, 59% came from closer than 150 km to NMCH (Table 3.2).

Fourteen patients had a functioning KT for at least four months, with a mean duration of having a functional KT during the study period of 27 months (5 – 36 months). Of these, 10/14 (71%) came from closer than 150 km to NMCH, and 4/14 (29%) came from further than 150 km from NMCH. Of the KT patients, 50% were Stable KT patients (Table 3.2)

Table 3.1 The demographic details of the cohort

Category	Number (n = 55)
Sex:	
Male	30
Female	25
Race:	
Black	48
White	3
Asian	3
Mixed	1
Diagnosis:	
CAKUT	17
Nephrotic syndrome	15
Primary hyperoxaluria	4
Glomerulonephritis	4
HIV nephropathy	3
Lupus nephritis	2
Haemolytic uraemic syndrome	1
Unknown	9

Table 3.2 The number of patients (PD, HD, KT) in the intervention and the comparator

	Intervention	Comparator
Total number (n = 55)	33 (60%)	22 (40%)
PD (n = 21)	10 (48%)	11 (52%)
HD (n = 39)	23 (59%)	16 (41%)
KT (n = 14)	7 (50%)	7 (50%)

3.2 Transition probabilities

In addition to the data from NMCH, referral and evaluation outcome data were available from PH, RCWMCH, IALCH, SBAH, CHBAH, DGMAH, UAH, and CMJAH. All the numbers represent an estimated value averaged over the previous four years, except for data from NMCH which were actual data derived retrospectively from both hard copy files, and electronic medical records, as described in the methods.

An average number of 6.37 (3 – 9) new cases of ESKD present for evaluation across South Africa each year, representing entry into State A (Table 3.3). Of these, on average 0.83 (0 – 1.5) are turned down due to distance alone (Table 3.4), giving a transition probability of 0.87 $[(6.37 - 0.83)/6.37]$ for the transition from State A to State B, and 0.13 $(0.83/6.37)$ for the transition from State A into State F for the comparator.

It was assumed that no child in the intervention would be denied entry into the program due to distance alone, giving a transition probability of 1 for the transition from State A to State B for the intervention.

An average number of 2.88 (1.3 – 4.83) new cases (Table 3.5) are turned down per year due to medical and social reasons, giving a transition probability of 0.45 $(2.88/6.37)$ for movement from State B to State F for both the comparator and the intervention.

Table 3.3 The estimated number of new cases of ESKD presenting to the divisions of paediatric nephrology in the State Sector per year for evaluation

New ESKD cases per year	Mean	Min	Max
NMCH	9	6	14
IALCH	5	2	8
UNIVERSITAS	5	2	8
SBAH	5	3	8
CHBAH	3	1	3
RCWMCH	13	8	17
PH	5	2	7
<i>Nationwide average</i>	<i>6.37</i>	<i>3.43</i>	<i>9.29</i>

Table 3.4. The estimated number of new cases rejected due to distance from hospital

Cases rejected per year	Mean	Min	Max
NMCH	1	0	2
IALCH	0	0	0
UNIVERSITAS	1	0	2
SBAH	1	0	2
CHBAH	0	0	0
RCWMCH	2	0	3
<i>Nationwide average</i>	<i>0.83</i>	<i>0</i>	<i>1.5</i>

Table 3.5. The estimated number of new cases rejected due to medical and social reasons including distance from hospital

Cases rejected per year	Mean	Min	Max
NMCH	2	1	3
IALCH	2	1	4
UNIVERSITAS	4	2	5
SBAH	4	3	7
CHBAH	1	0	2
RCWMCH	4	1	8
<i>Nationwide average</i>	<i>2.88</i>	<i>1.3</i>	<i>4.83</i>

Complete data to enable the calculation of the transition probabilities for the unidirectional movement from State B to States C and D, for the bidirectional movement from State C to States D and E, from State D to States C and E, and from State E to States C and D, as well as the data for the unidirectional movement from States C, D, and E, to State F, were available from the records of all 55 NMCH patients included in the study.

The probabilities for the movement from State B to State C and from State B to State D were determined separately for the group of children who came from closer than 150 km to NMCH (the Intervention) and for the group who came from further than 150 km from NMCH (the comparator).

The transition probabilities together with their alpha and beta values for each state of the comparator, and of the intervention, are reflected in Table 3.6 and Table 3.7 respectively.

In Table 3.8, these transition probabilities for States C, D, and E, are compared to those reported in the two studies in Yang *et al*'s SR (29) which used the states PD, HD, KT, and Death, for their Markov models, and which also recorded their transition probabilities explicitly for each state in the paper (125)(127). Unlike our paper, neither of the papers reported on the probabilities of their patients' pre KRT program journey (*viz* States A and B in our model) (125)(127).

Table 3.6. The transition probabilities and the *alpha* and *beta* values for the comparator

Description 1	Description 2	Probability	<i>SE</i>	<i>Distribution</i>	<i>alpha</i>	<i>beta</i>
State A to State A	ESKD - ESKD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State B	ESKD - Referred	0.87	0.12	<i>Beta</i>	5.53	0.83
State A to State C	ESKD - PD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State D	ESKD - HD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State E	ESKD to KT	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State F	ESKD to Death	0.13	0.12	<i>Beta</i>	0.83	5.53
State B to State B	Referred - Referred	0.00	0.00	<i>Beta</i>	0.00	5.53
State B to State C	Referred - PD	0.23	0.16	<i>Beta</i>	1.26	4.27
State B to State D	Referred - HD	0.32	0.18	<i>Beta</i>	1.77	3.77
State B to State E	Referred - KT	0.00	0.00	<i>Beta</i>	0.00	5.53
State B to State F	Referred - Death	0.45	0.19	<i>Beta</i>	2.50	3.03
State C to State C	PD - PD	0.67	0.09	<i>Beta</i>	18.50	9.31
State C to State D	PD - HD	0.26	0.08	<i>Beta</i>	7.17	20.64
State C to State E	PD - KT	0.00	0.00	<i>Beta</i>	0.00	27.82
State C to State F	PD - Death	0.08	0.05	<i>Beta</i>	2.14	25.68
State D to State C	HD - PD	0.08	0.04	<i>Beta</i>	3.91	47.64
State D to State D	HD - HD	0.85	0.05	<i>Beta</i>	43.93	7.62
State D to State E	HD - KT	0.02	0.02	<i>Beta</i>	1.13	50.42
State D to State F	HD - Death	0.05	0.03	<i>Beta</i>	2.58	48.96
State E to State C	KT - PD	0.00	0.00	<i>Beta</i>	0.00	20.64
State E to State D	KT - HD	0.11	0.07	<i>Beta</i>	2.29	18.34
State E to State E	KT - KT	0.89	0.07	<i>Beta</i>	18.34	2.29
State E to State F	KT - Death	0.00	0.00	<i>Beta</i>	0.00	20.64

Table 3.7. The transition probabilities and the *alpha* and *beta* values for the intervention

Description 1	Description 2	Probability	<i>SE</i>	<i>Distribution</i>	<i>alpha</i>	<i>beta</i>
State A to State A	ESKD - ESKD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State B	ESKD - Referred	1.00	0.00	<i>Beta</i>	6.37	0.00
State A to State C	ESKD - PD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State D	ESKD - HD	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State E	ESKD - KT	0.00	0.00	<i>Beta</i>	0.00	6.37
State A to State F	ESKD - Death	0.00	0.00	<i>Beta</i>	0.00	6.37
State B to State B	Referred - Referred	0.00	0.00	<i>Beta</i>	0.00	6.37
State B to State C	Referred - PD	0.21	0.15	<i>Beta</i>	1.31	5.06
State B to State D	Referred - HD	0.34	0.17	<i>Beta</i>	2.18	4.19
State B to State E	Referred - KT	0.00	0.00	<i>Beta</i>	0.00	6.37
State B to State F	Referred - Death	0.45	0.18	<i>Beta</i>	2.88	3.49
State C to State C	PD - PD	0.67	0.09	<i>Beta</i>	18.50	9.31
State C to State D	PD - HD	0.26	0.08	<i>Beta</i>	7.17	20.64
State C to State E	PD - KT	0.00	0.00	<i>Beta</i>	0.00	27.82
State C to State F	PD - Death	0.08	0.05	<i>Beta</i>	2.14	25.68
State D to State C	HD - PD	0.08	0.04	<i>Beta</i>	3.91	47.64
State D to State D	HD - HD	0.85	0.05	<i>Beta</i>	43.93	7.62
State D to State E	HD - KT	0.02	0.02	<i>Beta</i>	1.13	50.42
State D to State F	HD - Death	0.05	0.03	<i>Beta</i>	2.58	48.96
State E to State C	KT - PD	0.00	0.00	<i>Beta</i>	0.00	20.64
State E to State D	KT - HD	0.11	0.07	<i>Beta</i>	2.29	18.34
State E to State E	KT - KT	0.89	0.07	<i>Beta</i>	18.34	2.29
State E to State F	KT - Death	0.00	0.00	<i>Beta</i>	0.00	20.64

Table 3.8. A comparison of the mean transition probabilities with some of those from the literature

Description 1	Description 2	<i>Comparator</i>	<i>Intervention</i>	<i>Moradpour</i> (125)	<i>Villa</i> (127)
State A to State A	ESKD - ESKD	0.00	0.00	-	-
State A to State B	ESKD - Referred	0.87	1.00	-	-
State A to State C	ESKD - PD	0.00	0.00	-	-
State A to State D	ESKD - HD	0.00	0.00	-	-
State A to State E	ESKD - KT	0.00	0.00	-	-
State A to State F	ESKD - Death	0.13	0.00	-	-
State B to State B	Referred - Referred	0.00	0.00	-	-
State B to State C	Referred - PD	0.23	0.21	-	-
State B to State D	Referred - HD	0.32	0.34	-	-
State B to State E	Referred - KT	0.00	0.00	-	-
State B to State F	Referred - Death	0.45	0.45	-	-
State C to State C	PD - PD	0.67	0.67	0.76	0.7025
State C to State D	PD - HD	0.26	0.26	0.075	0.0975
State C to State E	PD - KT	0.00	0.00	0.04	0.12
State C to State F	PD - Death	0.08	0.08	0.125	0.08
State D to State C	HD - PD	0.08	0.08	0.0665	0.068
State D to State D	HD - HD	0.85	0.85	0.795	0.795
State D to State E	HD - KT	0.02	0.02	0.0035	0.068
State D to State F	HD - Death	0.05	0.05	0.135	0.1325
State E to State C	KT - PD	0.00	0.00	0.003	0.0035
State E to State D	KT - HD	0.11	0.11	0.035	0.035
State E to State E	KT - KT	0.89	0.89	0.945	0.9445
State E to State F	KT - Death	0.00	0.00	0.017	0.017

3.3 Pharmacy, NHLS, and SANBS costs

A complete set of costing data was available for all except 3/10 of the PD group from closer than 150 km away, 2/11 of the PD group from further than 150 km away, 1/16 of the HD group from further than 150 km away, and 1/10 of the Unstable KT group. These seven patients were excluded from the costing analysis leaving a total of 16 patients with complete costing data in the PD group, 38 with complete costing data in the HD group, and 13 with complete costing data in the KT group, from whose data the cost analysis was performed.

For these patients, the mean total cost per patient per year (PC + NHLS + SANBS) for the whole cohort was ZAR 179 661 (*SD*: 105 790).

The total mean cost per patient per year (PC + NHLS + SANBS) for the children from closer than 150 km from NMCH was ZAR 229 307 (*SD* 202 850) which was statistically significantly less than the mean total cost for the children from further than 150 km from NMCH, viz ZAR 501 322 (*SD*: 424 847) (p .002299).

The total mean cost per patient per year for the children on PD was ZAR 267 561 (*SD*: 133 071) which was statistically significantly more than the total mean cost per patient per year for the children on HD, viz ZAR 156 581 (*SD*: 115 895) (p .00004) (Table 3.9).

The total mean PC per patient per year for the children on PD was ZAR 194 692 (*SD*: 100 210) which was statistically significantly more than the total mean PC per patient per year for the children on HD, viz ZAR 99 259 (*SD*: 33 257) (p < .00001) (Table 3.9).

The total mean NHLS cost per patient per year for the children on PD was ZAR 42 170 (*SD*: 20 689) which was statistically significantly more than the total mean NHLS cost per patient per year for the children on HD, viz ZAR 26 440 (*SD*: 20 368) (p 0.006) (Table 3.9).

There was no statistically significant difference in the total mean SANBS costs per patient per year between the PD and HD groups (Table 3.9).

Table 3.9. A comparison of the mean total cost (ZAR) per year, as well as the mean pharmacy cost, the mean NHLS cost, and the mean SANBS cost, for the PD and the HD groups

	Peritoneal dialysis (n = 16)				Haemodialysis (n = 38)				<i>p</i>
	Min	Mean	SD	Max	Min	Mean	SD	Max	
Total	84 511	267 561	133 071	515 514	89 815	156 581	115 895	368 031	.0004
PC	59 890	194 692	100 210	414 569	34 458	99 259	33 257	183 935	.00001
NHSL	10 329	42 170	20 689	94 551	3 606	26 440	20 368	125 119	.006
SANBS	0	30 700	40 817	153 010	0	22 264	31 511	177 615	NS

NS – Not significant

Of the PD group, 6/16 (37.5%) had uncomplicated PD courses and required only between zero and three months of HD until their PD was established, while 10/16 (62.5%) had complicated PD courses needing, on average, 11.2 months (*SD*: 6.58) of HD while on PD.

The total mean cost per patient per year for the children on PD who needed less than 3 months of HD was ZAR 180 714 (*SD*: 63 454), which was statistically significantly less than that of the PD group who needed three months or more of HD, viz ZAR 319 670 (*SD*: 138 676) (*p* .02).

In addition, the total mean PC per patient per year for the children on PD who needed less than 3 months of HD was ZAR 129 912 (*SD*: 44 825) which was also statistically significantly less than that of the PD group who needed three months or more of HD, viz ZAR 233 560 (*SD*: 105 567) (*p* .02).

There was no statistically significant difference in the NHSL and SANBS costs of these two groups, or in their number of days spent in hospital. There was also no statistically significant difference between the mean total and PC costs of the children on PD who needed less than 3 months of HD and the HD group.

For all the children who had a KT, the mean total cost per patient per year was ZAR 138 941 (*SD*: 122 221). This was statistically significantly less than the mean total cost per patient per year of the PD group (p .006144) but was not statistically significantly different to the mean cost per patient per year of the HD group.

Of the 13 children who had a KT, 6/13 had medical courses that were complicated by multiple admissions and by having to go back onto dialysis within the time frame of the study. The total mean cost per patient per year for these six “*Unstable KT*” patients, who represent the comparator, was ZAR 223 890 (*SD*: 138 676). This was statistically significantly more than the total mean cost per patient per year of the seven “*Stable KT*” patients, who represent the intervention, who did not need any admissions, and whose graft function remained stable during the study, viz ZAR 66 128 (*SD*: 21 173) (p .006134).

The total mean cost per patient per year of the seven “*Stable KT*” patients was statistically significantly less than the above total mean PD cost per patient per year (p .000382), the above total mean HD cost per patient per year (p .000129), and the total mean cost of the HD and PD patients combined, viz ZAR 189 464 (*SD*: 100 248) (p .001033).

When breaking down the costs of the HD and PD patients of the intervention group and of the comparator group for the purposes of the model, there were no statistically significant differences between the mean PC, NHLS, and SANBS costs of each group (Table 3.10).

However, when breaking down the costs of the “*Stable KT*” and the “*Unstable KT*” patients into their PC, NHLS, and SANBS costs for the purposes of the model, there were statistically significant differences noted between the mean PC, NHLS and SANBS costs of the two groups (Table 3.10).

Table 3.10. A comparison of the mean costs (ZAR) per year of both groups for each of the three modes

	Intervention				Comparator				<i>p</i>
	Min	Mean	<i>SD</i>	Max	Min	Mean	<i>SD</i>	Max	
PD PC	90 034	171 692	86 710	349 992	59 890	212 580	111 208	414 569	NS
PD NHLS	10 329	36 063	15 548	53 383	19 116	46 920	23 733	94 551	NS
PD SANBS	0	12 158	9 772	21 375	5 504	45 121	50 173	153 010	NS
HD PC	58 579	95 079	29 014	183 935	34 458	105 668	39 083	176 344	NS
HD NHLS	11 024	35 796	24 774	125 485	17 739	33 930	13 760	68 796	NS
HD SANBS	0	25 144	38 681	177 615	0	17 847	15 443	50 275	NS
KT PC	12 026	23 394	11 124	42 349	22 905	45 263	19 919	76 844	.014
KT NHLS	31 374	41 500	12 381	66 642	29 405	111 113	52 413	182 143	.003
KT SANBS	0	1 610	1 419	3 340	0	67 513	82 817	225 482	.029

NS – Not significant

3.4 Length of stay

The mean in-hospital LOS for the whole cohort was 73 days per year (*SD*: 71.42).

The mean LOS for the patients from less than 150 km away was 57 days per year (*SD*: 68.08), which was statistically significantly less than the overall mean LOS for the children from more than 150 km away from NMCH, viz 98 days per year (*SD*: 70.83), (*p* .018743).

There was no statistically significant difference between the overall mean LOS for the whole PD cohort, 144 days (*SD*: 97) per year, and the whole HD cohort, viz 96 days (*SD*: 67) per year.

There was no statistically significant difference between the mean LOS of the group of children on PD who came from closer to, and further away from, 150 km from NMCH (Table 3.11), and there was also no statistically significant difference in the LOS of the children on PD who needed less than 3 months of HD and that of the PD group who needed three months or more of HD.

However, four of the PD group (1/10 from the group less than 150 km from NMCH, and 3/11 of the group from further than 150 km from NMCH) did not need admission to hospital during the data collection period. Excluding these four patients, and only analysing the mean LOS data of the children on PD who needed admission to hospital during the data collection period, the children on PD from closer than 150 km from the hospital had a mean LOS of 103 days per year (*SD*: 55) which was significantly less than that of the children from further away than 150 km, viz 182 days per year (*SD*: 102), (*p* .03).

There was a statistically significant difference between the mean LOS of the children on HD who came from closer to 150 km from NMCH, 74 days per year (*SD*: 55), and those from further away from 150 km from NMCH, viz 127 days per year (*SD*: 71) (*p* .01) (Table 3.11).

Children with a KT spent on average 53 days (*SD*: 69) in hospital per year which was statistically significantly less than the mean number of days spent in hospital by both the HD group (*p* .023406) and the PD group (*p* .025463).

There was also a statistically significant difference between the mean LOS of the “*Stable KT*” group, 2 days per year (*SD*: 2.7), and the mean LOS of the “*Unstable KT*” group, viz 82 days per year (*SD*: 33) (p .000028) (Table 3.11).

Table 3.11. A comparison of the mean in-hospital length of stay of both groups for each of the three modes (days per year)

	Intervention				Comparator				<i>p</i>
	Min	Mean	<i>SD</i>	Max	Min	Mean	<i>SD</i>	Max	
PD	0	93	61	177	0	133	121	334	<i>NS</i>
HD	5	74	55	206	48	127	71	270	<i>.01</i>
KT	0	2	2.7	7	31	82	33	125	<i>.000028</i>

NS – Not significant

3.5 Time spent at Marang House

Of the children who lived closer than 150 km from the hospital, statistically significantly fewer of the group spent time at MH, 7/33 (21%), as compared to those from further away than 150 km, 11/22 (50%), (p .025).

Only 1/21 (5%) of the PD cohort (a child from further than 150 km) spent time at MH while on PD. That patient stayed there for 4.92 months. As compared to the PD cohort, statistically significantly more of the HD cohort, 17/39 (44%), spent time at MH while on HD (p .002).

Of the 23 children on HD who came from closer than 150 km away, statistically significantly less, 7/23 (30%), spent time at MH, as compared to those who came from further away than 150 km, 10/16 (63%), (p .046).

The mean duration of stay at MH while on HD was 8.25 months. This was the same for the children who came from closer than 150 km and further than 150 km from NMCH.

None of the KT patients spent time at MH while they had a functional KT.

The costing data, the LOS data, the probability of a child being admitted to MH, the MH LOS, and the MH cost per year data, were used to inform the values used in the Markov model. They are recorded in Table 3.12 for the comparator, and Table 3.13 for the intervention.

Table 3.12. The costs (ZAR) per year for each state, the in-hospital and MH LOS, the probability of needing an admission to MH, and the *alpha* and *beta* values used in the model for the comparator

Description	Mean	SE	Distribution	Alpha	Beta
<u>State A</u>					
Workup @ PH	37 668	4 805	<i>gamma</i>	61	613
<u>State B</u>					
Workup @ NMCH	23 543	4 805	<i>gamma</i>	24	981
<u>State C - PD Costs</u>					
PD Pharm cost	111 208	37 069	<i>gamma</i>	9	12 356
PD NHLS cost	23 733	7 911	<i>gamma</i>	9	2 637
PD SANBS cost	50 173	16 724	<i>gamma</i>	9	5 575
PD LOS cost	624 505	400 708	<i>gamma</i>	2	257 110
PD MH cost	54 760	2 794	<i>gamma</i>	384	143
<u>State D - HD Costs</u>					
HD Pharm cost	105 668	10 091	<i>gamma</i>	110	964
HD NHLS cost	33 930	3 553	<i>gamma</i>	91	372
HD SANBS cost	17 847	3 987	<i>gamma</i>	20	891
HD LOS cost	597 773	266 658	<i>gamma</i>	5	118 952
HD MH cost	91 786	10 641	<i>gamma</i>	74	1 234
<u>State E - KT Costs</u>					
KT Pharm cost	45 263	9 960	<i>gamma</i>	20.65	2192
KT NHLS cost	111 113	26 206	<i>gamma</i>	17.98	6181
KT SANBS cost	67 513	41 408	<i>gamma</i>	2.66	25 397
KT LOS cost	386 223	113 627	<i>gamma</i>	11.55	33 429
KT MH cost	0	0	-	0	0
<u>Hospital LOS (days)</u>					
PD LOS	133	40.27	<i>gamma</i>	10.85	12.22
HD LOS	127	18.32	<i>gamma</i>	48.01	2.64
KT LOS	82	16.72	<i>gamma</i>	24.08	3.41
<u>MH LOS (months)</u>					
PD LOS at MH	5	0	<i>gamma</i>	0	0
Prob of MH on PD	0.09	0.08	<i>beta</i>	1	10
HD LOS at MH	8	1	<i>gamma</i>	48	0
Prob of MH on HD	0.63	0.12	<i>beta</i>	10	6

Table 3.13. The mean costs (ZAR) per year for each state, the in-hospital and MH LOS, the probability of needing an admission to MH, and the *alpha* and *beta* values used in the model for the intervention

Description	Mean	SE	Distribution	Alpha	Beta
<u>State A</u>					
Workup @ PH	37 668	4 805	<i>gamma</i>	61	613
<u>State B</u>					
Workup @ NMCH	23 543	4 805	<i>gamma</i>	24	981
<u>State C - PD Costs</u>					
PD Pharm cost	171 692	32 773	<i>gamma</i>	27	6 256
PD NHLS cost	36 063	5 877	<i>gamma</i>	38	958
PD SANBS cost	12 158	3 693	<i>gamma</i>	11	1 122
PD LOS cost	437 459	212 394	<i>gamma</i>	4	103 121
PD MH cost	0	0	-	0	0
<u>State D - HD Costs</u>					
HD Pharm cost	95 079	6 050	<i>gamma</i>	247	385
HD NHLS cost	35 796	5 166	<i>gamma</i>	48	745
HD SANBS cost	25 144	8 065	<i>gamma</i>	10	2 587
HD LOS cost	348 137	241 073	<i>gamma</i>	2	166 935
HD MH cost	91 759	17 626	<i>gamma</i>	27	3 386
<u>State E - KT Costs</u>					
KT Pharm cost	23 394	3 708	<i>gamma</i>	39.80	588
KT NHLS cost	41 500	4 127	<i>gamma</i>	101.11	410
KT SANBS cost	1 610	473	<i>gamma</i>	11.58	139
KT LOS cost	11 435	8 809	<i>gamma</i>	1.69	6785
KT MH cost	0	0	-	0	0
<u>Hospital LOS (days)</u>					
PD LOS	93	23.18	<i>gamma</i>	16.06	5.78
HD LOS	74	11.54	<i>gamma</i>	41.04	1.80
KT LOS	2	0.90	<i>gamma</i>	7.28	0.33
<u>MH LOS (months)</u>					
PD LOS at MH	0	0	-	0	0
Prob of MH on PD	0	0	<i>beta</i>	0	10
HD LOS at MH	8	1	<i>gamma</i>	72	0
Prob of MH on HD	0.30	0.09	<i>beta</i>	7	16

3.6 Cost effectiveness of the intervention

3.6.1 Deterministic analysis

The deterministic sensitivity analysis (DSA) calculated that, over 20 years, the intervention could be expected to incur a mean cost of ZAR 29 620 283 from the societal perspective, and of ZAR 28 928 795 from the healthcare payer perspective. In comparison, the comparator could be expected to incur a mean cost of ZAR 31 668 624 from the societal perspective, and of ZAR 31 175 013 from the healthcare payer perspective (Table 3.14).

The difference between these costs yielded an incremental cost from introducing the intervention of ZAR -2 048 341 from the societal perspective, and of ZAR -2 246 218 from the healthcare payer perspective (Table 3.14).

The model calculated that, over 20 years, the intervention could be expected to produce 26 QALYs, as compared to the comparator which was calculated to produce a mean of only 23 QALYs. The difference between the two yielded a net gain of three QALYs should the intervention be introduced (Table 3.14).

The model calculated that the ICER for the introduction of the intervention was ZAR -682 780 per QALY gained from the societal perspective, and ZAR -748 739 per QALY gained from the healthcare payer perspective (Table 3.14).

Table 3.14. The Costs, QALYs, ICERs, and INMBs of the deterministic analysis – the societal and the healthcare payer analyses (ZAR)

	Intervention		Comparator		Incremental		ICER	INMB
	Costs	QALYs	Costs	QALYs	Costs	QALYs		
Societal	29 620 283	26	31 668 624	23	-2 048 341	3	-682 780	2 384 341
Healthcare payer	28 928 795	26	31 175 013	23	-2 246 218	3	-748 739	2 582 218

For a WTP threshold of ZAR 112 000, the INMB of introducing the intervention was calculated to be ZAR 2 384 341 for the societal perspective, and ZAR 2 582 218 for the healthcare payer perspective.

A further sensitivity analysis was performed on the group of variables depicted in Figure 3.1 and Figure 3.2. These variables were analysed across a range of values to see which would generate the biggest changes to the ICER.

The variables which resulted in the largest change in the ICER are depicted in the Tornado Diagrams in Figure 3.1 for the societal perspective, and in Figure 3.2 for the healthcare payer perspective. LOS for the HD cohort, the number of new CKD cases per year from PH, and the LOS for the PD cohort contributed to the largest changes in the ICER.

Figure 3.1. The Tornado Diagram depicting the effect of changes in the input parameters on the INMB (ZAR) from the societal perspective

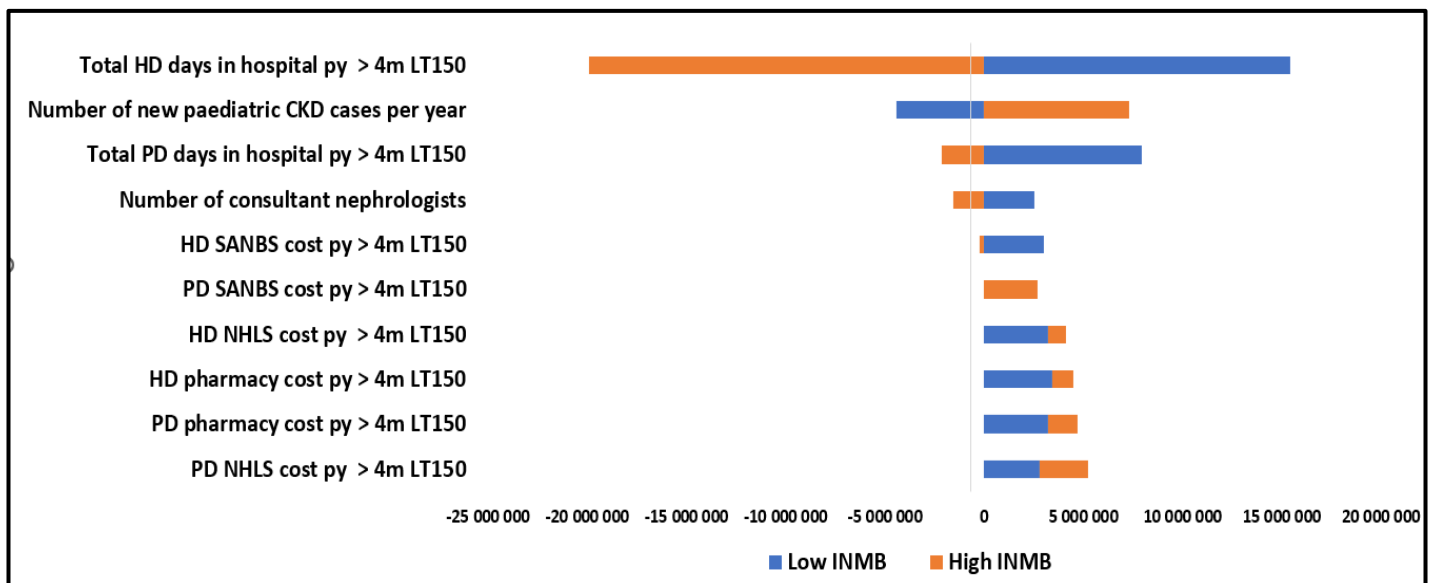
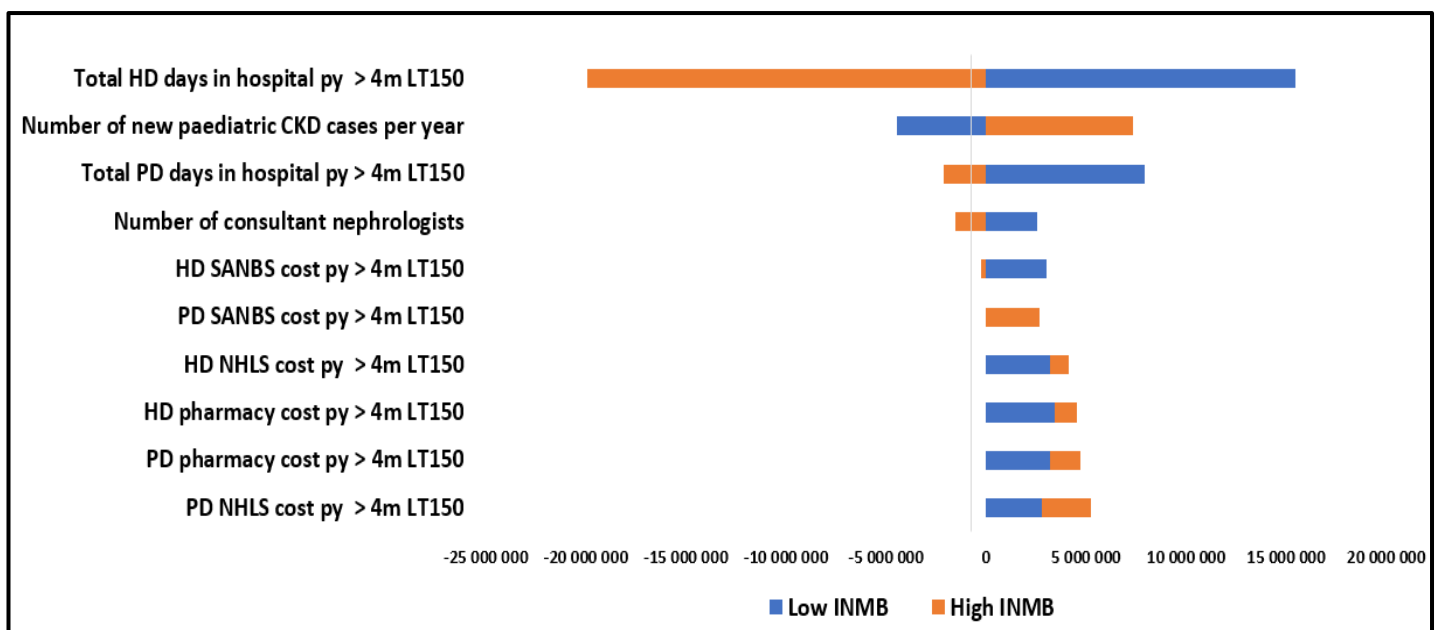


Figure 3.2. The Tornado Diagram depicting the effect of changes in the input parameters on the INMB (ZAR) from the healthcare payer perspective



3.6.2 Probabilistic sensitivity analysis

As depicted in Table 3.15 and Table 3.16, the probabilistic sensitivity analysis (PSA) calculated that, over 20 years, the intervention could be expected to incur a mean cost of ZAR 32 002 917 (*SD*: ZAR 19 278 385) from the societal perspective, and of ZAR 31 219 788 (*SD*: ZAR 18 746 417) from the healthcare payer perspective.

In comparison, the comparator could be expected to incur a mean cost of ZAR 34 759 729 (*SD*: ZAR 29 061 498) from the societal perspective, and of ZAR 34 216 817 (*SD*: ZAR 28 614 993) from the healthcare payer perspective.

The difference between these costs yielded an incremental cost from introducing the intervention of ZAR -2 756 812 (*SD*: ZAR 33 179 681) from the societal perspective, and of ZAR -2 997 029 (*SD*: ZAR 32 563 539) from the healthcare payer perspective.

As depicted in Table 3.15 and Table 3.16, the model predicted that over 20 years, the intervention could be expected to produce a mean of 27 QALYs (*SD*: 15), as compared to the comparator which was predicted to produce a mean of only 24 QALYs (*SD*: 15). The difference between the two yielded a net gain of three QALYs should the intervention be introduced.

Table 3.15. The Costs and QALYs of the probabilistic analysis – the societal perspective analysis (ZAR)

	Intervention		Comparator		Incremental	
	Costs	QALYs	Costs	QALYs	Costs	QALYs
Mean	32 002 917	27	34 759 729	24	-2 756 812	3
<i>SD</i>	<i>19 278 385</i>	<i>15</i>	<i>29 061 498</i>	<i>15</i>	<i>33 179 681</i>	<i>19</i>
<i>*CI</i>	<i>1 196 314</i>	<i>1</i>	<i>1 803 402</i>	<i>1</i>	<i>2 058 955</i>	<i>1</i>

***The mean +/- CI give the range in which the costs lie**

Table 3.16. The Costs and QALYs of the probabilistic analysis – the healthcare payer perspective analysis (ZAR)

	Intervention		Comparator		Incremental	
	Costs	QALYs	Costs	QALYs	Costs	QALYs
Mean	31 219 788	27	34 216 817	24	-2 997 029	3
SD	18 746 417	15	28 614 993	15	32 563 539	19
*CI	1 163 303	1	1 775 694	1	2 020 720	1

***The mean +/- CI give the range in which the costs lie**

The model calculated that the ICER for the introduction of the intervention was ZAR -918 937 per QALY gained from the societal perspective, and ZAR -999 010 per QALY gained from the healthcare payer perspective.

The ICER Scatter Plot graphs from the probabilistic analysis for both the societal and the healthcare payer perspective are depicted in Figure 3.3 and Figure 3.4 respectively.

Both graphs show that the ICERs generated by the model fall into the Northeast (NE) and Southwest (SW) quadrants of ICER scatter plot.

Figure 3.3 The ICER Scatter Plot from the societal perspective

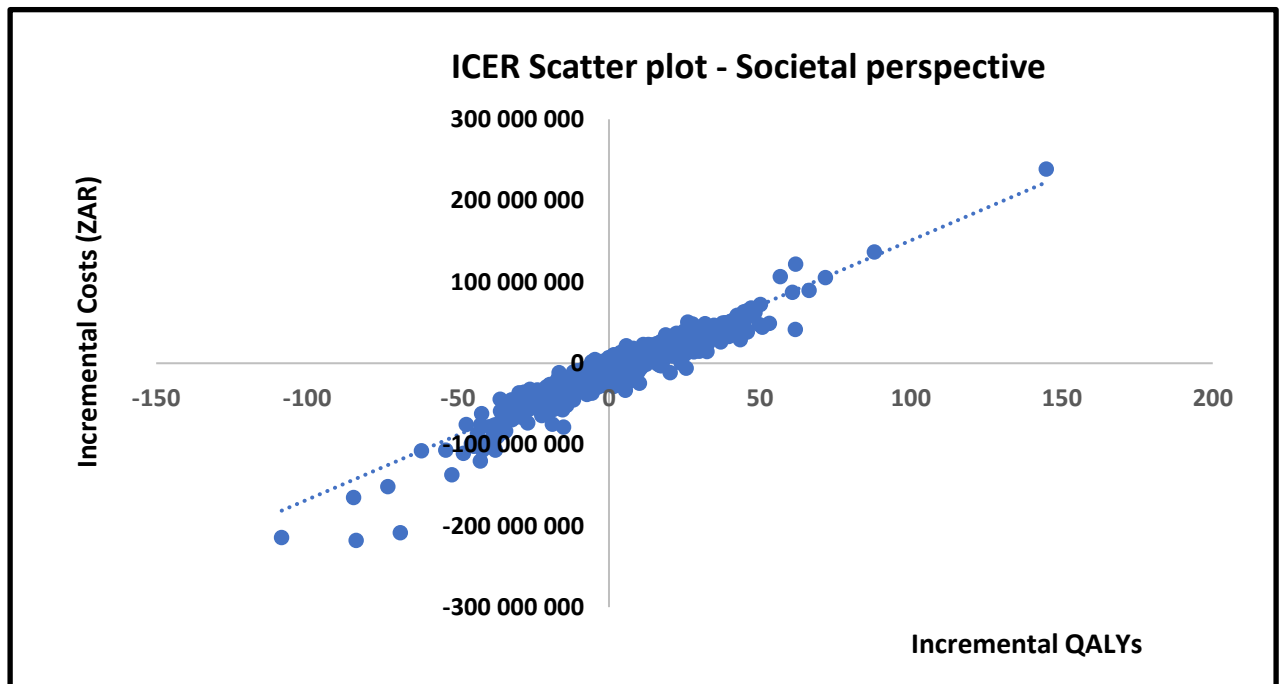
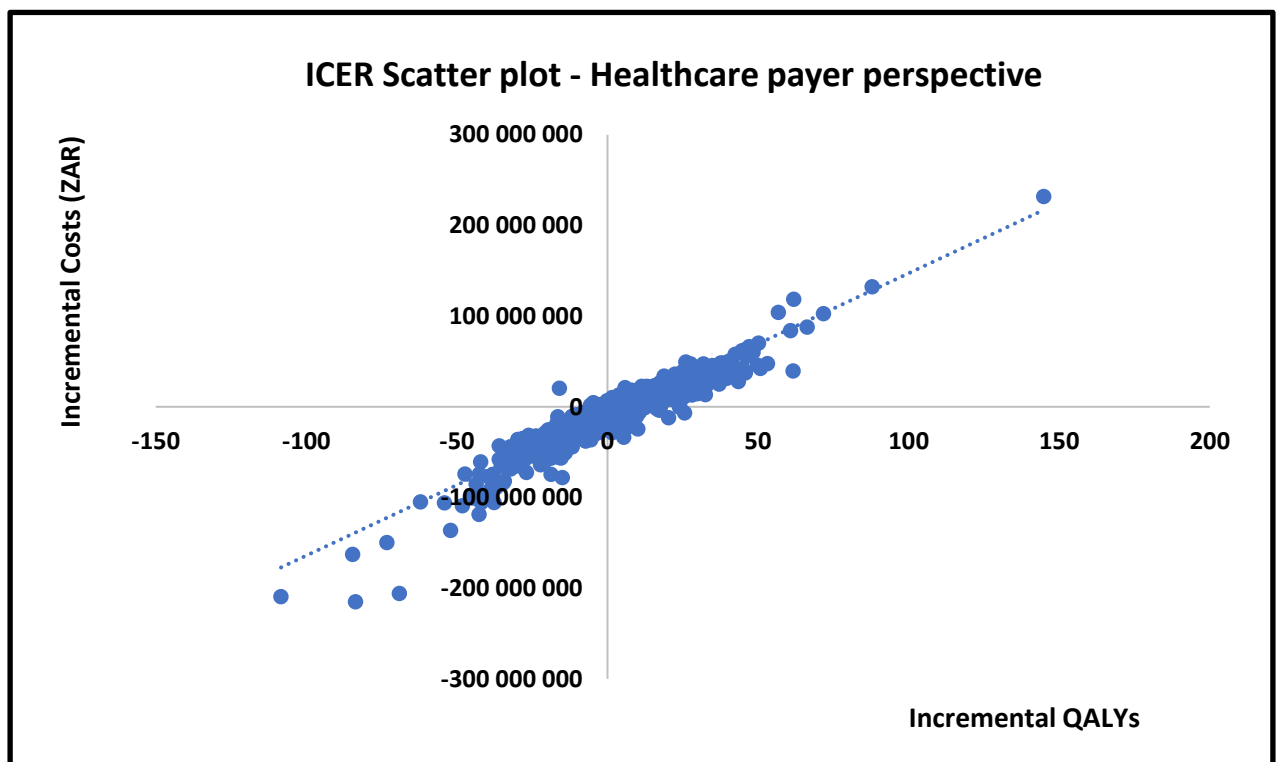


Figure 3.4 The ICER Scatter Plot from the healthcare payer perspective



For a WTP threshold of ZAR 112 000, the INMB of introducing the intervention was calculated to be ZAR 3 092 812 for the societal perspective, and ZAR 3 333 029 for the healthcare payer perspective

To determine the likelihood of the intervention being cost effective, we calculated the probability of cost-effectiveness at different willingness to pay thresholds (ranging from zero to ZAR 1 000 000) for both societal and healthcare payer perspectives.

When charting the probability of the intervention being cost effective against a range of WTP thresholds, the CEACs generated demonstrate that the intervention is likely to be cost effective more than 50% of the time from a WTP of ZAR 112 000. This holds true for both the societal perspective (Figure 3.5) and for the healthcare payer perspective (Figure 3.6).

Figure 3.5 Graph depicting the CEAC from the societal perspective

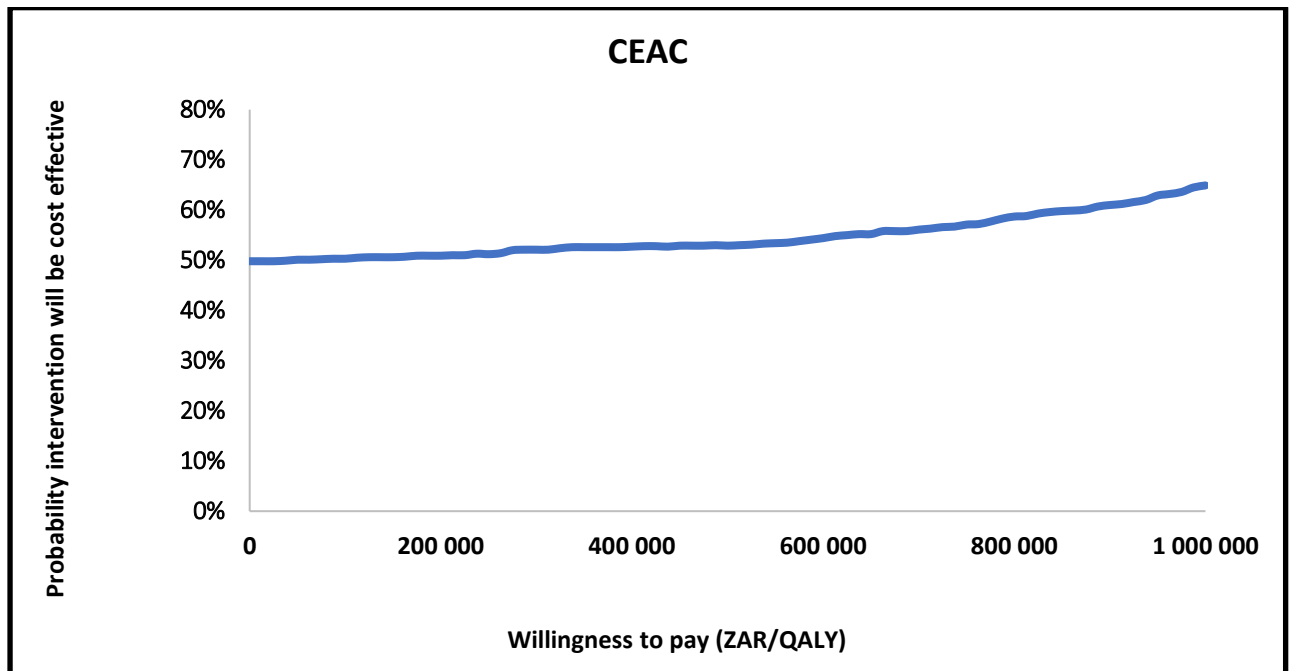
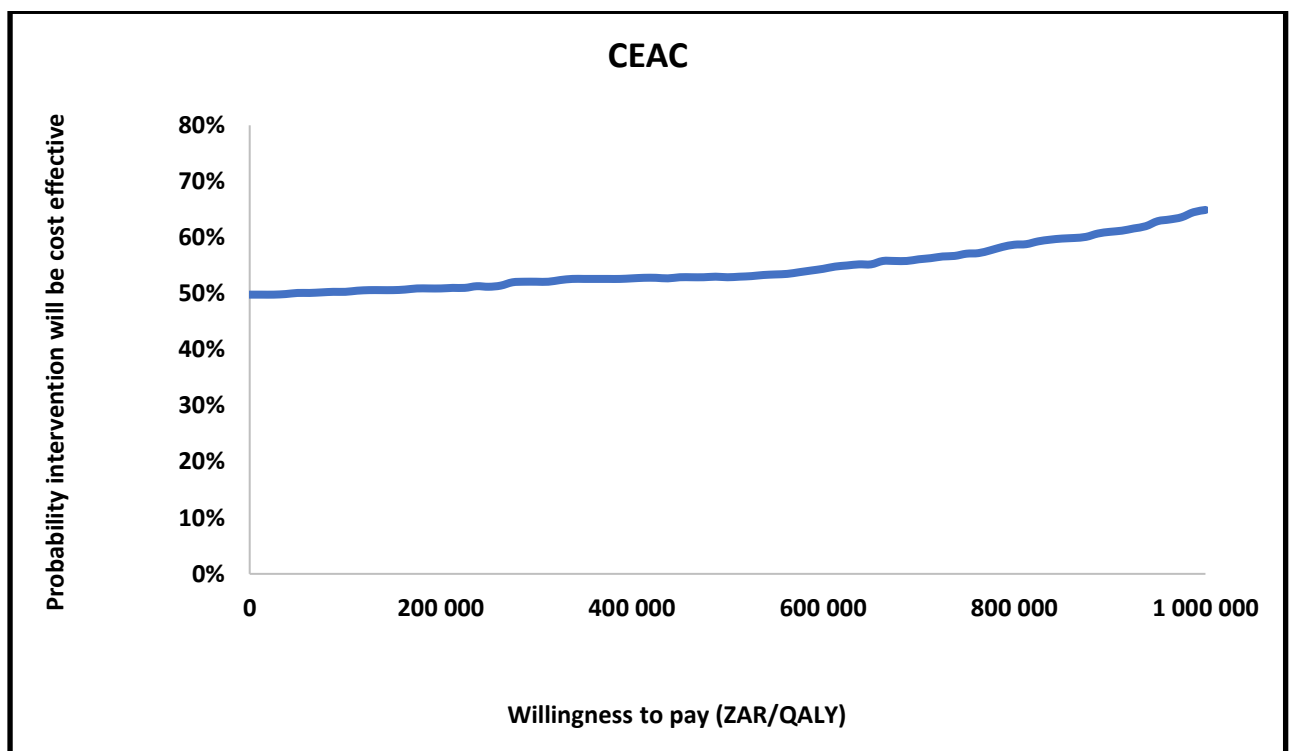


Figure 3.6 Graph depicting the CEAC from the healthcare payer perspective



CHAPTER FOUR

DISCUSSION

This chapter discusses the Results of the study in the context of both the international and the local literature. It also presents the strengths and the limitations of the study.

4.1 Discussion

The study set out to determine whether it would be cost effective for children with ESKD from PH to be initiated on KRT at NMCH, and to then be transitioned back to a satellite unit at PH for follow up and treatment. The reason for proposing this model was that satellite centre based care has been shown to increase quality of life, improve access, and decrease LOS, for patients who live at a distance from tertiary centres (44)(45). Satellite units have also been shown to be cost effective (47)(48), especially from the societal perspective in other parts of the world (49).

As elaborated on in the Introduction, Drummond *et al* define an EE as “*the comparative analysis of alternative courses of action in terms of both their costs and their consequences*” (51). In line with this, we set out to analyse whether our intervention, namely the establishment of a satellite unit at PH for children who came from the PH area, would be more cost effective than our comparator, *viz* the current status quo, where these children are managed at NMCH.

Two recent systematic reviews address the cost of KRT (29)(33). Of the two, Yang *et al* specifically selected studies that compared all three of the main forms of KRT namely PD, HD, and KT (29). For this reason, much of the Discussion revolves around comparing the data of this study to that presented by Yang *et al* (29).

A Markov model was used to perform a CUA using the societal as well as the healthcare payer perspectives. Except for the utility scores assigned to the different states of the model, all the data for the variables used in our model came, as recommended (52), from local South African data. In comparison, in Yang *et al*, eight of the ten studies deemed suitable for inclusion in their SR used Markov modelling (29). However, only three studies were conducted from the societal perspective, and none of the studies obtained their own data for their analyses (29).

Our study used data collected on cost, LOS, and health effects, from 55 patients. While some centres have reported data obtained from between 12 and 126 patients per centre (125)(126)(130)(136), the number of patients from which our data was obtained compares favourably with those from similar studies reported from LMICs such as South Africa and Brazil (141)(142). In these two cases, Makhele *et al* collected data from 46 adult patients (141), and Camargo *et al* collected data from 30 children (142).

Our cohort's demographic profile conforms with recent data on paediatric CKD published from South Africa (173), and matches that currently seen in state paediatric dialysis facilities around the country (personal communication with the Divisional Heads of Paediatric Nephrology at all academic centres offering tertiary paediatric nephrology services across the country).

The most common primary diagnosis in our cohort was CAKUT followed by steroid resistant nephrotic syndrome. This clinical patient profile is in keeping with data published from both Europe (11), South America (142), and from South Africa (12)(13).

The mean distance of the whole group from home to NMCH was 149 km which reflects that the drainage area of our unit includes Gauteng, Limpopo, North-West, and Mpumalanga. As PH is situated 312 km from Johannesburg (5), we used the mean distance from the patient's home to NMCH to divide our cohort into the two groups for the purposes of the study.

Unlike similar studies in the literature which obtained their transition probabilities from expert opinion and the literature (125), or from national or international registries (127)(129)(132), our study derived its transition probabilities from verified, though as yet unpublished, local data.

As is apparent from our data for State A and for State B, while the probability of a child who presents with ESKD being referred on for evaluation is over 85%, almost half of these children will not be accepted into the programs on offer. This is in keeping with previously published data from South Africa (1). Reasons for this phenomenon include late presentation, large distances from tertiary centres, and the predicted inability of the patient's family to cope with the high demands of the programs available (18)(21).

The likelihood of our patients failing PD, and having to transition to HD, is higher than that noted by Moradpour and Villa (125)(127). However, our finding is in keeping with previously published South African data (192)(193), and is thought to be related mainly to the poor socio-economic conditions in which our patients and their families find themselves, and to the fact that our low KT rate leads to longer times on dialysis (20)(192)(193).

While our patients' probability of mortality while on PD is lower than that reported by Moradpour (125), it is similar to that reported by Villa (127). In addition, the mortality probability of our patients on HD, and of those with a KT, are lower than those reported by Moradpour and Villa (125)(127). These findings may be related to the fact that the cohorts in Moradpour (125) and Villa (127) were made up of mainly adult patients, while our cohort is made up of children. Children have been shown to have improved rates of survival while on KRT as compared to adult patients (173)(194)(195).

The probability of one of our patients being offered a KT is lower than that reported by Moradpour and Villa (125)(127). This is keeping with the trend that, although the Western Cape has managed to maintain its transplant rate per year for state funded children, over the past few years fewer and fewer kidney transplants are being done per year on state funded paediatric patients from the Johannesburg/Gauteng program (personal communication with the Divisional Heads of Paediatric Nephrology at all academic centres offering tertiary paediatric nephrology services across the country). Reasons postulated for this phenomenon include a high rate of rejection of potential live donors due to medical issues, and a nationwide shortage of deceased donor kidneys (20).

As indicated in the Methods section, we collected primary data on the PC, the NHLS costs, and on the SANBS costs, for each patient in the cohort. These costs were then added together to provide a single direct medical cost estimate for each patient. Then, in the two models, the costs were added to the LOS, the estimated staff costs, the travel cost, and the cost of the time spent at MH, for the various analyses.

There was a significant difference between the total mean cost per patient per year for the children who lived closer than 150 km to NMCH, and those who lived further than 150 km from NMCH. This pattern, in which the patients who lived closer than 150 km to the hospital (representing the intervention) cost less than those who lived further than 150 km from the

hospital (representing the comparator) repeated itself throughout the analysis. The pattern is in keeping with findings from other authors that receiving KRT at a centre closer to home is more cost effective than receiving it at a centrally based service (47)(48)(49).

Our data showed that the total mean cost per patient per year for the children on PD was significantly more than the total mean cost per patient per year for the children on HD. A breakdown of this cost showed that it was due to the mean PC per patient per year for the children on PD, and the total mean NHLS cost per patient per year for the children on PD, being significantly more than those of the children on HD.

While this finding, that PD is more expensive than HD, is in keeping with some studies from around the world (140), as well as from South Africa (6)(137), it is not in keeping with other international (136) and South African (142) data which show that, typically, PD is more cost effective than HD.

Malatji *et al* postulated that the higher cost of PD in their study may have been due to the additional costs of transporting PD supplies across Limpopo (6). In our case, our Chief Pharmacist has speculated that there are two possible reasons for the high PC of our PD patients; the first is that, for patient safety reasons, the NMCH Pharmacy and Therapeutics Committee policy does not allow PD consumables, which have been delivered to the patient's home, to be brought back for use in-hospital during an admission. This leads to the extra ordering of PD consumables during an admission. The second is that premature ordering and delivery of PD consumables to the child's home, before the child had been fully established on PD and discharged, may also have resulted in the extra ordering of PD consumables.

Of the PD group, 62.5% had complicated PD courses as evidenced by their needing more than three months of HD to establish PD. The mean total cost per patient per year for this group was significantly more than that of the group with a less complicated course. This difference in cost came from the significant difference in the mean PC of the two groups, with the PC of the less complicated group being significantly less than the PC for the more complicated group, giving credence to our Chief Pharmacist's hypothesis above.

There was no statistically significant difference between the mean total and PC costs of the uncomplicated children on PD and the HD group, suggesting that uncomplicated PD, while not cheaper than HD, would not cost more than HD.

We speculate that the higher NHLS cost of the PD group may have been related to the high percentage of the PD group who had complicated PD courses. These children would have, *de facto*, needed more laboratory based special investigations given their complicated clinical course.

The total mean cost per patient per year of the seven “*Stable KT*” patients was significantly less than both the total mean PD cost per patient per year, the total mean HD cost per patient per year, and the total mean cost of the HD and PD patients combined. In addition, there were significant differences noted between the PC, NHLS, and SANBS costs of the “*Stable KT*” and the “*Unstable KT*” groups, with the “*Unstable KT*” group having significantly higher PC, NHLS, and SANBS costs, than the “*Stable KT*” group.

This finding, that stable KT patients cost less than other modes of KRT, is in keeping with data from other centres (136)(142). In Yang *et al* (29), when KT was compared to the other modes of KRT, KT was also more cost effective than both PD and HD (125).

The role played by distance from hospital and mode of KRT on LOS was evident from the results. The study found that the mean LOS for patients from less than 150 km away was significantly less than the mean LOS for the children from more than 150 km away from NMCH. In addition, the mean LOS of the children on PD who came from closer than 150 km, and who needed admission to hospital, was significantly less than that of the children on PD who came from further away than 150 km from NMCH, and who needed admission to hospital. There was also a significant difference between the mean LOS of the children on HD who came from closer to 150 km from NMCH and those from further away than 150 km from NMCH.

Children on KRT will often develop complications such as infections, fluid overload, and access catheter issues (20). While some of these issues will require a hospital admission, many of them can be addressed by daily, or alternate day, visits allowing them to stay at home while the problem is resolved on an outpatient basis (20). This option is not available for children who live far from the hospital as the travel time to and from NMCH, and lack of experience

and expertise at their local hospital level, make frequent outpatient review impractical (20). As a result, many of the children treated at NMCH who stay at a distance from the hospital are routinely be admitted for issues that could be managed as an outpatient had the hospital been situated closer to their homes.

These findings are in keeping with other observations from the literature that children who live further away from hospital in general, and those with paediatric CKD in particular, will have longer LOS than their counterparts (36)(37).

All children with a KT spent significantly less days in hospital than both the HD group and the PD group. In addition, the mean LOS of the “*Stable KT*” group was also significantly less than that of the “*Unstable KT*” group. This data is also in keeping with data from the literature showing that KT is superior to other forms of KRT when it comes to quality of life and cost (24)(26).

Although children with complex medical conditions who have to live in medical foster care have been shown to have lower quality of life scores than their counterparts who live with their parents (39), Marang House has been life-saving for many patients by giving them a place to stay while they await a KT (40). Our results highlight this fact by showing the significant role that MH plays in the lives of the children in this cohort who live far from NMCH, especially for those on HD who need therapy three times a week. Of the children who lived closer than 150 km from the hospital, significantly fewer spent time at MH as compared to those from further away than 150 km. Stable PD patients receive their therapy at home, and so only one patient of the PD cohort (a child from further than 150 km) needed to spend time at MH as compared to 44% of the HD cohort who needed to spend time at MH. Of the 23 children on HD who came from closer than 150 km away, significantly less spent time at MH as compared to those who came from further away than 150 km.

Understandably, none of the KT patients spent time at MH while they had a functional KT as they were all well enough to live at home with their families.

The DSA predicted that, over 20 years, the intervention could be expected to be cost saving from both the societal and the healthcare payer perspectives. The model also predicted that, over 20 years, the intervention could be expected to yield a net gain of QALYs. The ICERs for the introduction of the intervention imply that the intervention is considered to “dominate”, in that it is more cost effective than the alternative (155).

A classic CET is the one initially promoted by WHO-CHOICE of one to three times the gross domestic product (GDP) per capita (163). Although these CETs may be too high for some countries, leading to a possible overestimation of the cost effectiveness of an intervention when used for EE, they have become widely adopted, especially in low- and middle-income countries (161). As such, the WTP threshold for the model was set at one times the GDP per capita for South Africa in 2022 (ZAR 112 000). For this WTP, the deterministic model findings imply that it would be recommended that the intervention take precedence over the comparator (155).

The sensitivity analysis showed that the variables which resulted in the greatest change in the ICER for both perspectives were the LOS of the HD and PD patients, and the number of new cases referred per year. This finding emphasises the role played by LOS on the costs generated by our patients and highlights the potential effect of a change in the number of new ESKD patients entering the system each year. While the numbers of new paediatric ESKD patients being referred into the system locally, and across the country, have remained relatively constant over the past five years, a large increase in the number of new referrals, which might accompany the establishment of a new KRT service in the area, may well impact negatively on our results.

Because probabilistic analysis takes into account a range of values that the parameters are likely to take, it provides the analyst with a more correct estimate of the net benefits than that of a DSA (171). For this reason, a PSA was also performed. Using a WTP of ZAR 112 000, the INMBs generated by the PSA for both the societal and the healthcare payer perspectives also suggest that the intervention takes precedence over the comparator as suggested by the DSA results above.

The PSA for both the societal and the healthcare payer perspectives showed that the ICERs generated by the model fell into the Northeast (NE) and Southwest (SW) quadrants of the ICER Scatter Plots suggesting that while the intervention is likely to be more effective than the comparator, it might also cost more.

To explore this further, when calculating the probability of cost-effectiveness at different WTP for both the societal and the healthcare provider perspectives, the probabilistic analysis demonstrated that the intervention is likely to be cost effective at a WTP of ZAR 112 000. This applied to both the societal perspective and the healthcare payer perspectives. This lends support to our finding that a satellite KRT service would be cost effective in the South African

environment. Our finding is also in keeping with data from the literature which show that not only do satellite dialysis units improve access for people who live at a distance from tertiary centres (44)(45), but they are also cost effective (47)(48)(49).

Of note is that our findings are in contrast with Ferguson *et al* (136). Ferguson *et al* reported that providing dialysis therapy in a rural setting could be almost four times the cost of providing therapy in bigger urban settings (50). However, the primary reason given for the high cost of the satellite units in Ferguson *et al* was the inability of the rural units to maintain the full use of their available bed capacity (50). It is unlikely that, given the severe shortage of state KRT facilities in our region (20), underuse of any satellite state dialysis centre will be of concern in the South African setting.

4.2 Strengths

The study has several strengths. The topic under investigation focused on a real and relevant challenge faced by our unit every day, and it addresses a question that is of both practical and current importance. This is true especially when given the challenges of accessing this type of therapy for patients coming from rural areas, and the cost of healthcare in general in South Africa.

The study conforms to the methodologies recommended by the CHEERS 2022 guidelines (54). This makes it both reproducible and of practical use to other researchers, readers, and policy makers.

By using a CUA we were able to compare the costs and benefits of our intervention in a way that addressed the questions of both technical, and allocative, efficiency. In addition, the study was performed from both the societal and the healthcare payer perspectives, giving us the widest possible insight into the costs and consequences of our intervention.

The use of a Markov model gave us the opportunity to accommodate the progress of our patients through the various health states of the model over time. The cycle lengths and time horizon allowed for all the main costs and health consequences to be considered, and the model gave us the opportunity to discount future benefits and costs, so that financial resources spent

or saved in future years could be considered by people using our findings to make program decisions.

Using a DSA and a PSA for our analysis gave us the opportunity to address the issues of stochastic, parameter, and structural uncertainty, and allowed us to analyse a range of values that our parameters were likely to take. This gave us a much more accurate estimate of the net benefits of our intervention. It also gave us the opportunity to estimate, and to present, the probability that each alternative might be cost effective.

The size of the cohort at NMCH, the similarity of the demographic and clinical picture of the cohort to other paediatric dialysis units in SA, and the fact that the unit at NMCH treats such a high proportion of children who need KRT across South Africa, make it very likely that our results are representative of most South African children with ESKD seeking care in the public health sector.

Our transition rates through the different States of the model are, for the most part, an accurate reflection of the journey of a child with ESKD in the public health sector in South Africa. This, combined with the fact that our cost and LOS data were collected from a recent and relatively large cohort of patients, makes our results and conclusions both relevant and current to decision makers in this country.

4.3 Limitations

The study also has several limitations that should be noted and considered when interpreting the results.

The utility scores that were used for each state in the model were obtained from international studies, and therefore may not reflect those of South African children with ESKD. In addition, while we believe that our transition rates for States A, B, C, and D, are very representative of all children undergoing treatment for ESKD in the public health sector in South Africa, this is not true for State E (KT). The Western Cape continues to have a higher-than-average rate of KT per year than do the other provinces, and this effect should be considered when applying the results of this study to similar services in the Western Cape.

While the cost data relating to the cost per day in hospital, the costs incurred in running a dialysis unit, and the cost of transport to the family for the various modes of KRT, were all obtained from data published from South Africa (21)(141)(143), they were not directly captured by the primary investigator. They therefore may not be completely applicable to this cohort and may have biased our results.

It appears that the cost per day in hospital reported by Ramjee would have included those of the PC, NHLS, and SANBS costs (143). To compensate for this, we used the lower average cost per day of a representative mix of public sector facilities, as reported by Ramjee, rather than the higher average cost per day of a state tertiary hospital for our cost per day variable. Nevertheless, it is possible that we have underestimated the cost per day in hospital for each of our patients.

While the accuracy of the cost and LOS data collected by the primary investigator was repeatedly checked and verified, because of the retrospective nature of the data it is possible that errors in the assignment of the cost and LOS data to the various States for each patient may have crept in.

Stochastic uncertainty and heterogeneity apply to patient data collected from a sample of the population as part of a study (166), and so any uncertainty related to estimates based on our sample will be inversely related to the size of our sample (166). It is therefore important to note that, despite the relatively large size of our sample in comparison to other single centre studies of a similar nature, the large SDs of our cost and LOS data indicate that there is a significant amount of uncertainty around our estimates. This uncertainty is most likely related to the size of our sample and should be taken into account when applying our results to other projects.

While we believe that our results accurately reflect the journey of children with ESKD in the public health sector in South Africa, it is possible that the transition rates, costs, and LOS, data of our cohort do not reflect those of privately funded patients around the country, or those from other LMIC countries in Sub-Saharan Africa and elsewhere. As a result, our results should be used with caution when generalising them to other cohorts.

To allow for a direct comparison of our cost data to those discussed in the literature, an attempt was made to isolate the PC and LOS costs of chronic KRT from the various studies cited in the

Introduction. Unfortunately, differences in methodology, and in the classification and reporting of the costs by the different authors, made an accurate comparison almost impossible. Therefore, although our finding that satellite unit KRT is likely to be cheaper than a centralised service is in keeping with findings elsewhere in the literature, we were unable to directly compare our PC and LOS data to those from these other studies.

We attempted to conduct our study from both the societal and the healthcare payer perspectives. However, we recognize that it is difficult to fully evaluate all the societal costs of any program in general, and of our program in particular. We used the estimated cost of the families' travel expenses, as well as the cost of a stay at MH, to expand our evaluation beyond that of the direct cost to the hospital. However, we acknowledge that these two variables are a very weak surrogate for the expected real costs to society of our proposed intervention. We did not take direct medical costs arising from out-of-pocket medical costs, or direct non-medical costs, such as those related to the need to procure food, accommodation, or child-care, into account. We also did not take indirect costs, such as those related to time lost from work or school, or the services of informal carers, into account either.

In addition, even if, as we have assumed, the adult unit at PH has enough infrastructure and capacity to accommodate the needs of the intervention without the need for any extra capital expenditure, the opportunity cost of a new patient taking up a dialysis slot, that will now be unavailable to someone else, has also not been taken into account.

CHAPTER FIVE

CONCLUSION

This chapter provides a summary of the findings, the conclusion, and a few recommendations.

5.1 Summary

We postulated that decentralising paediatric nephrology services would go a long way to relieving the burden on children with ESKD, and their families. To evaluate this hypothesis the study set out to investigate whether it would be cost effective to establish a satellite paediatric dialysis centre at PH from both the healthcare payer, and the societal perspectives. We used the current state, in which there is no paediatric dialysis facility at PH and all children from that area who are accepted onto our program are treated at NMCH, as the comparator.

The cost of PD was significantly more than that of HD. This appeared to be due to higher PC and NHLS costs related to this mode of KRT. We speculated that this may have been due to the extra ordering of PD consumables and the long LOS of those children with complicated PD. This theory was supported by our finding that there was no difference in cost between uncomplicated PD patients and the HD group.

Our findings confirm that KT is the best form of KRT in terms of cost, LOS, and the need for away-from-home accommodation.

The role played by distance from hospital and mode of KRT on LOS was evident from the results for all three modes of KRT. Our results confirmed that those patients who live closer to a KRT centre would have a lesser need for a facility like Marang House. The results highlighted the important role played by Marang House in the care of our patients, and the potential benefit of establishing a satellite service closer to our patients' homes.

The DSA calculated that the intervention could be expected to yield a positive INMB for a WTP threshold set at one times the average GDP per capita for South Africa in 2022 (ZAR 112 000) for both the healthcare payer and the societal perspectives. The variables which resulted

in the largest change in the ICER were LOS and the number of new ESKD patients entering the system each year.

The PSA calculated an ICER of ZAR -918 937 per QALY gained from the societal perspective, and of ZAR -999 010 per QALY gained from the healthcare payer perspective and, for a WTP of ZAR 112 000, the PSA found the INMB of introducing the intervention to be ZAR 3 092 812 for the societal perspective, and ZAR 3 333 029 for the healthcare payer perspective. In addition, when calculating the probability of cost-effectiveness at different WTP thresholds for both societal and healthcare payer perspective, the CEACs generated demonstrated that the intervention is likely to be cost effective more than 50% of the time for a WTP threshold of ZAR 112 000, or one times the average GDP per capita for South Africa in 2022. This applied to both the societal perspective and the healthcare payer perspectives.

5.3 Conclusions

Our findings are in keeping with data from the literature which show that satellite KRT units can be cost effective. Establishing a satellite unit at PH for the treatment of children with ESKD in the area would not only improve access to life saving KRT for these children, but it would also improve their quality of life in that they would be able to live at home, rather than at a medical foster facility such as Marang House. Our findings show that the establishment of a satellite paediatric KRT unit at PH is likely to be cost effective from both the healthcare payer and the societal perspectives.

5.2 Recommendations

It would have been useful had there been South African specific utility scores for paediatric CKD available. This is something that future research should address.

Although the information we obtained on paediatric KRT across the country was readily available, it has not yet been published. We recommend that the South African paediatric nephrology community collaborate to publish this very important data in a relevant scientific journal.

Our data confirmed that KT is much more cost effective than other forms of KRT. These findings highlight that identifying and addressing the root causes of the decline in the number of public health sector paediatric KT performed in our area should be flagged as a priority

We demonstrated that a satellite paediatric KRT unit at PH could be cost effective from both the healthcare payer and the societal perspectives, and we believe that the creation of such a unit has the potential to reduce the cost burden on families of children from Limpopo with ESKD. The establishment of such a unit would also improve the quality of life of children who come from this area and who are in need of KRT. As such, we recommend that the Limpopo Department of Health use this study as part of a discussion around the establishment of a satellite KRT service for children at PH. We hope that our findings will encourage the introduction of, at least, a pilot program at PH to establish the validity of our results.

Success with this model at PH could then be used as a template to roll out similar projects across the region so that ‘distance from hospital’ will no longer be a reason to deny this life saving treatment to a child with ESKD.

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7. APPENDICES

Appendix 1. Plagiarism declaration

 
UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG
FACULTY OF
HEALTH SCIENCES

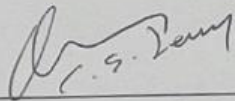
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Cecil Steven Levy (Student number: 8402569) am a student
registered for the degree of Master of Public Health in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 22 February 2024

Appendix 2. Ethics approval from the Wits HREC


UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG

R14/49 Dr C Levy

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200116

NAME: Dr C Levy
(Principal Investigator)

DEPARTMENT: School of Public Health
Medical School
University

PROJECT TITLE: An economic evaluation of the establishment of a
paediatric dialysis unit at Pietersburg Hospital,
Polokwane, Limpopo

DATE CONSIDERED: 2020/01/31

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr I Edoka

APPROVED BY: 
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2020/10/22

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary on the 3rd Floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in January and will therefore reports and re-certification will be due early in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

23/10/2020
Date

Appendix 3. Ethics approval certificate from IALCH



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

OFFICE OF THE MEDICAL MANAGER

Private Bag X03, Mayville, 4058

800 Vusi Mzimela (Bellair) Road, Mayville, 4091

Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

22 June 2021

Dr C Levy
School of Public Health
Medical School
University

Dear Dr Levy

Re: Approved Research: Ref No: M200116: An economic evaluation of the establishment of a paediatric dialysis unit at Pietersburg Hospital, Polokwane, Limpopo.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

The Secretariat
Health Research & Knowledge Management
330 Langaliballe Street, Pietermaritzburg, 3200
Private Bag X9501, Pietermaritzburg, 3201
Tel: 033395-3123, Fax 033394-3782
Email: hrkm@kznhealth.gov.za

Yours faithfully

.....
Dr A Harrichandparsad
Clinical Care Manager

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Appendix 4. Ethics approval from the Limpopo DOH



LIMPOPO

PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP_2020_10_031
Enquires : Ms PF Mahlokwane
Tel : 015-293 6028
Email : Kurhula.Hlomane@dhsd.limpopo.gov.za

Cecil Levy

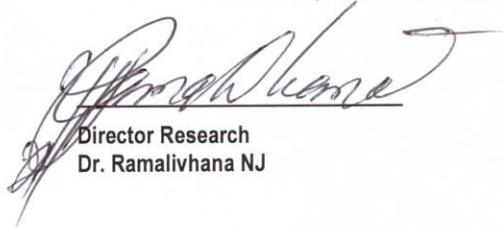
PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;

AN ECONOMIC EVALUATION OF THE ESTABLISHMENT OF A PAEDIATRIC DIALYSIS UNIT AT PIETERSBURG HOSPITAL, POLOKWANE, LIMPOPO

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
 - a. Present this letter of permission to the institution supervisor/s a week before the study is conducted.
 - b. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
 - c. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
 - d. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
 - e. The approval is only valid for a 1-year period.
 - f. If the proposal has been amended, a new approval should be sought from the Department of Health
 - g. Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated



Director Research
Dr. Ramalivhana NJ



Date

Private Bag X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: <http://www.limpopo.gov.za>

The heartland of Southern Africa – Development is about people!

Appendix 5. Letter of communication to Makhele *et al* (141) *re* the inclusion of the cost of a nephrologist/consultant in their study

From: Cecil Levy <Cecil.Levy@nmch.org.za>
Sent: 10 August 2023 10:53
To: makhele.nolo@gmail.com <makhele.nolo@gmail.com>; Brian Godman <brian.godman@strath.ac.uk>; Brian Godman <brian.godman@ki.se>; Brian Godman <brian.godman@outlook.com>
Subject: A cost analysis of haemodialysis and peritoneal dialysis for the management of end-stage renal failure at an academic hospital in Pretoria, South Africa

Dear Prof Godman and Dr Makhele, I hope that this email finds you both well.

I am a paediatric nephrologist working at the Nelson Mandela Children's Hospital in Johannesburg. I am also enrolled in the Wits School of Public Health MPH (Health Economics) program (Student number: 8402569), and I am in the process of completing my thesis.

The thesis is entitled "An economic evaluation of the establishment of a paediatric dialysis unit at Polokwane Hospital, Polokwane, Limpopo", and it aims to evaluate the theoretical cost effectiveness of establishing a paediatric dialysis unit at Polokwane Hospital, using the current state of no paediatric dialysis facility at that hospital as the comparator. I am using a Markov model to evaluate the difference in cost, and have used your paper (Makhele L, Matlala M, Sibanda M, Martin AP, Godman B. A cost analysis of haemodialysis and peritoneal dialysis for the management of end-stage renal failure at an academic hospital in Pretoria, South Africa. *PharmacoEconomics-open*. 2019 Dec;3:631-41) for the fixed and semi-variable costs of a state facility dialysis unit my model.

If I may, please could I clarify something with you about your paper's method? In the paper, the semi-variable costs are said to include the staff wages as per Box 1 (of the Appendix). Box 1 lists these staff costs as nursing costs, phlebotomist costs, physicians including anaesthetists, social workers, and dieticians. Box 1 then refers the reader to Table 2 in the text for details. Table 2 of the paper lists the staff members as follows: nursing assistant, dialysis nurse, registrar, nurse, social worker, phlebotomist, and anaesthesiology per hour. While Box 1 seems to imply that the list would include the wages of a consultant or specialist nephrologist, the list in Table 2 does not explicitly list this cost.

In the public service in South Africa, at most academic hospitals, tertiary care, like kidney replacement therapy or dialysis, is usually supervised by a consultant or specialist nephrologist. I was hoping you could clarify for me whether the semi-variable costs cited in your study do indeed include those of a specialist nephrologist/consultant or not.

I apologise for the trouble, but having this information will enable me to know whether I should make provision to add the cost of a consultant or specialist nephrologist to my model.

Thanking you in advance,

Dr Cecil Levy
Head of Unit - Renal

Tel: +27 (0)10 133-0728



Appendix 6. Reply from Makhele *et al* (141) *re* the inclusion of the cost of a nephrologist/consultant in their study

From: Letlhogonolo Makhele <letlhogonolo.makhele@smu.ac.za>
Sent: Tuesday, 15 August 2023 10:06
To: Cecil Levy <Cecil.Levy@nmch.org.za>
Cc: Molehi Matlala <molehi.matlala@smu.ac.za>
Subject: RE: A cost analysis of haemodialysis and peritoneal dialysis for the management of end-stage renal failure at an academic hospital in Pretoria, South Africa

*** This message is from an EXTERNAL SENDER - be CAUTIOUS, particularly with links and attachments ***

Good day Dr Levy

Thank you for the engagement.

The study approach was a prospective observational micro costing and site specific. We included in the calculations what was seen by the researcher at the site during data collection. It's a fact that the Nephrologists would have been part of the team especially in the diagnosis of the patient. That assumption could have been made, even though this was not observed during the study.

Suggestion:
Add as a fixed cost (assume hours) for diagnosis and then as a variable or semi variable (an hour is enough) depending on the current practice.

Best wishes!

Kind regards



Mr. Makhele Letlhogonolo (B.pharm, M.pharm)
Lecturer: School of Pharmacy
Course Coordinator: Post Graduate Diploma in Hospital Pharmacy Management
Sefako Makgatho Health Sciences University (SMU)
P.O.Box 156 | Medunsa | 0204 | South Africa
Tel: +27 (0) 12 521 4214 Tel: 082 073 1337
Sefako Makgatho Health Sciences University | @SMU_SA | smu_sa | SMU TV

SEFAKO MAKGATHO HEALTH SCIENCES UNIVERSITY
Pursuing the frontiers for quality health services

Appendix 7. Correspondence from Mr B Bray, Marang House

From: Bob Bray <bob@maranghouse.org>
Sent: Friday, 25 March 2022 12:07 PM
To: Cecil Levy <Cecil.Levy@nmch.org.za>
Subject: Marang House cost per child

Good morning Cecil

Salome asked me to forward you our cost structure per child.

This is difficult to precisely calculate. Most of our costs are fixed such as salaries, rental, insurance, transport etc whether we have one child or ten children. Also over the past year we have reduced our staff to the bare minimum because of the decrease in donations. This means that the cost per child has stayed more or less the same over the past three years.

I have calculated therefore, that, based on 8 children at Marang House, **the cost per child per month is R11 125**

If you need any further breakdown please let me know

Best regards

Bob Bray

Appendix 8. The VBA Macro

Sub Simulation()

'write the simulation code here, remember to begin and end with apostrophe. The basic structure of the macro is below'

'Important variables'

Dim cost_h_new As Double

Dim cost_h_old As Double

Dim cost_s_new As Double

Dim cost_s_old As Double

Dim qal_new As Double

Dim qal_old As Double

Dim i As Integer

Application.ScreenUpdating = False

' clear old results and replace with new simulation'

Sheets("simulation").Visible = True

Sheets("simulation").Select

Application.ScreenUpdating = False

Range("E7:j7").Select

Range(Selection, Selection.End(xlDown)).Select

Selection.ClearContents

Range("u7").Select

Range(Selection, Selection.End(xlDown)).Select

Selection.ClearContents

Sheets("Start page").Select

Application.ScreenUpdating = True

'switch to probabilistic model and insert a counter'

```
Range("prob") = 1  
Sheets("Start page").Select  
Application.ScreenUpdating = True  
Range("q14") = "iteration"  
Range("s14") = "of 1000"
```

```
For i = 1 To 1000
```

```
    Sheets("Start page").Select  
    Application.ScreenUpdating = True  
    Range("r14") = i
```

'then press F8 to iterate/sample variable values from the distribution'

Calculate

'get the results to sheet simulation'

```
cost_h_new = Range("total_costs_new_healthpayer")  
cost_h_old = Range("total_costs_old_healthpayer")  
cost_s_new = Range("total_costs_new_societal")  
cost_s_old = Range("total_costs_old_societal")
```

```
qal_new = Range("total_qalys_new")  
qal_old = Range("total_qalys_old")
```

```
Application.ScreenUpdating = False
```

```
Sheets("Simulation").Select  
Cells(6 + i, 5).Value = cost_h_new
```

```

Cells(6 + i, 6).Value = cost_s_new
Cells(6 + i, 7).Value = qal_new

Cells(6 + i, 8).Value = cost_h_old
Cells(6 + i, 9).Value = cost_s_old
Cells(6 + i, 10).Value = qal_old

'perform the iteration for a 1000 times'
Next i

'switch back to deterministic model to end simulation and delete the counter'
Range("prob") = 2
Sheets("Start page").Select
Application.ScreenUpdating = True
Range("q14:s14").Select
Selection.ClearContents

'CEAC'
Sheets("Simulation").Select
Dim wtp As Double
Dim prob_ce As Double

' do it 81 times

For i = 1 To 81

' copy new wtp
wtp = Cells(6 + i, 20)
Range("p2").Value = wtp

' copy prob_ce to column

```



```
prob_ce = Range("s4")
Cells(6 + i, 21).Value = prob_ce

Next i

Sheets("simulation").Visible = True

Sheets("Start page").Select
Application.ScreenUpdating = False
Range("a1").Select

MsgBox ("simulation complete")
End Sub
```

Appendix 9. The CHEERS checklist

CHEERS 2022 Checklist			
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page i: Title page, and Section 1.2 Research question, study aim, and the objectives
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page v: Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Section 1.1 Background, and Section 1.2 Research question, study aim, and the objectives
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Section 2.1 Study Design
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Section 3.1 Demographic details
Setting and location	6	Provide relevant contextual information that may influence findings.	Section 1.4 NMCH as the site of the study
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Section 2.1 Study Design
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Section 2.1 Study Design
Time horizon	9	State the time horizon for the study and why appropriate.	Section 2.1 Study Design

(continued)

Discount rate	10	Report the discount rate(s) and reason chosen.	Section 2.1 Study Design
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Section 2.1 Study Design
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Section 2.1 Study Design
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Section 2.1 Study Design
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Section 2.1 Study Design
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Section 2.1 Study Design and Section 2.2.3 Cost and LOS data
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Section 2.1 Study Design
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Section 2.3 Statistical Analysis and Section 2.4 Parameter Distributions
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Section 2.4 Parameter Distributions
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Section 2.4 Parameter Distributions

(continued)

Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Section 2.4 Parameter Distributions
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Section 2.2.2 Transition probabilities
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Table 2.1, Table 3.4, Table 3.5, Table 3.10, Table 3.11
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Table 3.12
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Section 3.6.1 Deterministic analysis and Section 3.6.2 Probabilistic sensitivity analysis
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Section 4.3 Limitations
Discussion			

(continued)

Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Section 4.1 Discussion, Section 4.2 Strengths, Section 4.3 Limitations
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Section 2.1 Study Design
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Section 2.1 Study Design

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

Appendix 10. The Turn-it-in report

