The feasibility, acceptability, and cost-effectiveness of using treatment monitors with a differentiated care approach to improve TB treatment adherence in South Africa

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A thesis submitted to the School of Public Health, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor of Philosophy

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Declaration

This thesis is submitted in the integrative narrative format, approved by the Faculty of Health Sciences.

I, **Rachel Mukora**, declare that this thesis is my original work. Where there has been contribution from other people, this has been duly acknowledged. It is being submitted for the degree of Doctor of Philosophy in Public Health in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.

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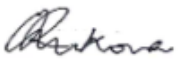
Signature: 

Date: 15 April 2025

Acknowledgements

To my supervisors, family, friends, and colleagues – thank you for all the years of support that you generously offered me while I embarked on this ambitious career milestone. I would also like to thank my employer, The Aurum Institute, and the funders of the TB MATE trial namely, Bill and Melinda Gates Foundation (BMGF), TB REACH and the Medical Research Council (MRC) South Africa for providing the financial resources that made this research possible.

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Executive summary

Background	Treatment success for drug-sensitive Tuberculosis (DS-TB) is defined as either those People With TB (PWTB) who have been cured or who have completed six months of treatment. The WHO recommended target level for treatment success is 90% while that of South Africa remains concerning at 79% for new and relapse cases registered in 2021. Some reasons for the low treatment success rates could be due to death, treatment failure, loss to follow-up (LTFU) or unevaluated treatment outcomes. Although public health facilities have strategies in place to improve adherence such as the Directly Observed Treatment Short Course (DOTS), treatment failure among PWTB still persists as a result of treatment interruptions. Non-adherence to treatment often leads to the development of drug resistant TB or a relapse in drug sensitive TB that are often difficult to treat requiring costly and toxic regimens creating further challenges to adherence. To accurately monitor TB treatment adherence new innovative methods in the form of digital adherence technologies (DATs) such as 99 DOTs, video DOT (VOT), ingestible sensors and electronic pill boxes have been introduced. Comprehensive evidence on the implications of DATs on a large scale is essential yet scarce. This evidence will guide policy decisions on which DAT to prioritize for successful large-scale implementation. Within the TB Monitoring and Adherence Endpoints pragmatic cluster-randomised trial, we evaluated an adherence monitoring and support system involving the Wisepill evriMED 1000 device (medication monitor) to inform a Differentiated Care Approach involving text messages, phone calls and home visits in three provinces of South Africa.
Overall Aim	To determine the feasibility, acceptability and cost-effectiveness as elements that are necessary for the successful implementation and policy buy-in of the adherence monitoring and support system.
Objectives	1.To describe the feasibility of implementing Wisepill evriMED device and differentiated care from a stakeholder perspective 2.To describe the acceptability of implementing Wisepill evriMED device and differentiated care from a PWTB perspective 3.To evaluate the cost-effectiveness of the intervention from a societal perspective

Methods	Feasibility: Feasibility of the intervention was explored using a guide with seven stakeholders from the Department of Health and 18 research assistants and facility staff. The sample size was selected on the basis of obtaining a representative sample while also considering saturation where themes usually start to converge after 15 interviews. Acceptability: We conducted 87 in-depth interviews with PWTB in local languages across three provinces. Interviews were audio recorded, transcribed verbatim and translated. Saturation was assessed during data collection and thematic analysis was used. Cost-effectiveness: We conducted a cost-effectiveness analysis from a societal perspective at one intervention and one control clinic per province (June 2019-August 2020). Provider costs were collected using a bottom-up activity-based costing approach involving time and motion studies. People with TB (PWTB) were interviewed on costs related to accessing the intervention. Adherence was measured using patients ≥80% adherence overall. Unit costs were calculated as cost per patient treated for TB while incremental cost-effectiveness ratio (ICER) was calculated as cost per additional adherent PWTB.
Results	Feasibility: PWTB appreciated being able to safely store their medication in the device. The reminders were helpful, although the features of the device such as the size, alarm and flashing lights created stigma as it was difficult to take treatment discreetly; especially for those who had not disclosed their TB diagnosis. Stakeholders were supportive of the intervention being integrated into the TB programme and were eager to be trained on the device as it helped monitor treatment adherence. However, there was distrust amongst stakeholders about pill intake even when device was opened, and device set-up was considered time consuming.

	Acceptability: PWTB attributed low value to sms but appreciated phone calls and had mixed views about home visits due to stigma. Stakeholders did not perceive any stigma created by the device but felt awareness on use of the device could be improved. Cost-effectiveness: The cost of achieving an additional adherent PWTB was estimated at $166.33. The sensitivity analysis showed that when each monitor is re-used for at least three times this reduces the health system cost from a range of $37.99 - $57.42 down to $21.73 - $41.17. Other ways of reducing health systems costs include negotiating a lower cost for the monitors with manufacturers and combined platform hosting for all DS-TB, DR-TB and TPT clients. DATs allows fewer clinic visits which reduces patients' productivity losses from missed work and non-medical costs such as transport.
Conclusions	Achieving people-centred TB care, including the introduction of DATs, will require that TB programmes incorporate patient insights to maximize their adoption and effectiveness. Medication monitors and DCA can be considered a cost-effective option for scale-up if we can reduce both health system costs and patient costs.

List of original papers

I submitted the following manuscripts (table 1) for publication in international journals. Results were also disseminated in the form of abstracts at both local and international conferences (table 2).

Table 1: Publication outputs

Manuscript
1. Qualitative study exploring the feasibility of using medication monitors and a differentiated care approach to support adherence among people receiving TB treatment in South Africa. ***Rachel Mukora***, *Noriah Maraba, Catherine Orrell, Lauren Jennings, Pren Naidoo, M Thulani Mbatha, Kavindhran Velen, Katherine Fielding, Salome Charalambous, Candice Maylene Chetty-Makkan* BMJ Open 2023;13:e065202. doi:10.1136/bmjopen-2022-065202
2. Acceptability of using the medication monitor and experience of a differentiated care approach for TB treatment adherence among people living with TB in South Africa ***Rachel Mukora***, *Barack Ahumah, Noriah Maraba, Catherine Orrell, Lauren Jennings, Pren Naidoo, Katherine L. Fielding, Kavindhran Velen, Salome Charalambous, Candice M Chetty-Makkan* PLOS Glob Public Health 3(10): e0001885. https://doi.org/10.1371/journal.pgph.0001885
3. Cost-Effectiveness Analysis of implementing Wisepill evriMED device and differentiated care approach in South Africa ***Rachel Mukora***, *Resignation Pelusa, Noriah Maraba, Catherine Orrell, Lauren Jennings, Pren Naidoo, Kavindhran Velen, Katherine L. Fielding, David Dowdy, Sedona Sweeney, Salome Charalambous* Under review in Frontiers in Medical Technology
4. Treatment adherence and clinical outcomes amongst drug-susceptible TB persons using medication monitor and differentiated care approach in South Africa: results from a cluster randomised trial. *Salome Charalambous, Noriah Maraba, Lauren Jennings, Israel Rabothata, Dolphina Cogill,* ***Rachel Mukora****, Piotr Hippner, Pren Naidoo, Nokhanyo Xaba, Lihle Mchunu, Kavindhran Velen, Catherine Orrell, Katherine L.Fielding* eClinical Medicine, Volume 75, September 2024. https://doi.org/10.1016/j.eclinm.2024.102745

Table 2: Conference presentations

Abstract	Conference	Presentation type
1. The feasibility and acceptability of using treatment monitors and a differentiated care approach to improve TB treatment adherence in South Africa	Union World Conference on Lung Health, October 2021	E-Poster
2. Patient acceptability of using medication monitors and experience of a differentiated care approach for TB treatment adherence in South Africa	Union World Conference on Lung Health, November 2022	Oral
3. Provider costs of using medication monitors and a differentiated care approach to improve TB treatment adherence in South Africa		E-Poster
4. The feasibility of using medication monitors and a differentiated care approach to improve TB treatment adherence in South Africa	South African TB Conference, September 2022	Oral
5. Acceptability of using medication monitors and experience of a differentiated care approach for TB treatment adherence in South Africa	Ekurhuleni Research Conference, November 2022	Oral
6. Provider costs of using medication monitors and a differentiated care approach to improve TB treatment adherence in South Africa		Poster
7. Cost-Effectiveness Analysis of implementing medication monitors and differentiated care approach in South Africa	Union World Conference on Lung Health, November 2023	Oral

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List of abbreviations

ART	Antiretroviral therapy
ASCENT	Adherence Support Coalition to End TB
CRF	Case Report Form
CQUIN	HIV Coverage, Quality, and Impact Network
DR-TB	Drug-resistant TB
DS-TB	Drug-sensitive TB
DATs	Digital Adherence Technologies
DOTs	Directly Observed Treatment Short Course
HCW	Healthcare Workers
HTA	Health Technology Assessment
HIV	Human Immunodeficiency Virus
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
IDI	In-depth Interview
LFTU	Loss to follow-up
LMICs	Low- and Middle-Income Countries
MTB	Mycobacterium Tuberculosis
NGO	Non-Governmental Organization
PHC	Primary Health Care
PhD	Doctor of Philosophy
PIS	Participant Information Sheet
PLHIV	People Living with HIV
PWTB	People With TB
SA	South Africa
SoC	Standard of Care
SMS	Short Message Service
TB	Tuberculosis
TB MATE	TB Monitoring Adherence to Treatment Endpoints
TPT	TB Preventive Therapy
USD	United States Dollar
VOT	Video DOT
WHO	World Health Organization
WTP	Willingness To Pay
ZAR	South African Rand

CHAPTER 1: BACKGROUND

1.1 Tuberculosis incidence, mortality and catastrophic costs

Tuberculosis (TB) is a widespread health problem where the global incidence in 2023 was reported at 133 per 100 000 population while the African region had an estimate of 208 per 100,000 [1]. South Africa (SA) reported a much higher incidence than both the global and the African region at 468 per 100 000 [1] while the prevalence was reported as 852 cases per 100 000 according to the national Prevalence survey [2]. Failure to address the TB epidemic leads to a catastrophic loss of lives and also catastrophic costs to People With TB (PWTB) and their households due to illness [3]. In SA, the TB mortality rate currently stands at 39 per 100,000 (as compared to the global rate at 14 per 100,000 amongst Human Immunodeficiency Virus (HIV) negative individuals), and 52 per 100,000 as compared to the global rate at 2.1 per 100,000 amongst those who are HIV positive [1]. According to the national TB Prevalence survey (2017-2019) conducted in SA, the prevalence was highest in people aged 35–44 years and those aged 65 years or older while the estimated prevalence was approximately 1·6 times higher in men than in women [2]. Figure 1 below shows the targets for the WHO END TB strategy and we see that globally the world (including SA) has fallen short of meeting the 2025 milestones [1].

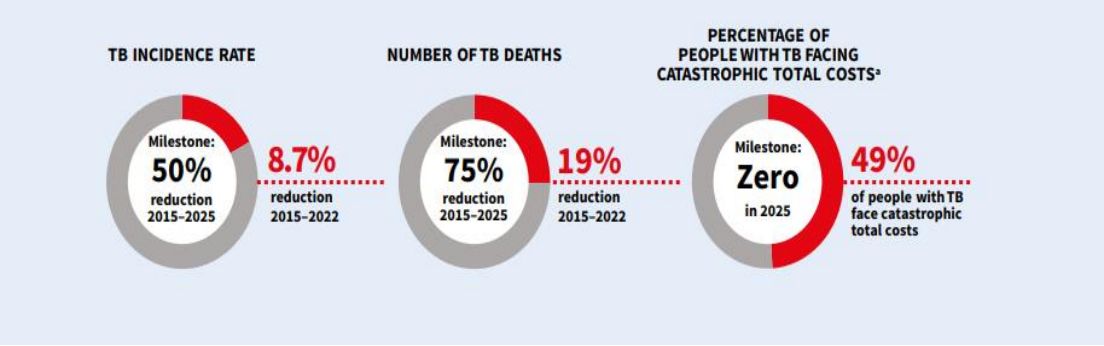

Figure 1: WHO END TB Strategy: 2025 milestones (source: Global TB report 2023)

There is an urgent need to identify those who are infected with TB and to provide treatment to them as a means of saving lives and halting the transmission of TB. The World Health Organization (WHO) has recommended treatment guidelines where people with TB (PWTB) adhere to a six month regimen and on completion are classified as either *treatment success* or *treatment failure* [4].

1.2 Gaps in the TB care cascade

The TB care cascade is made up of a series of steps which include the proportion of people who are tested from the general population, those who then receive a diagnosis, those PWTB who are initiated onto TB treatment and finally those who complete treatment [5]. At every step of the way there are significant drop-offs or gaps which need to be addressed using various strategies if the overall goal of halting TB transmission is to be achieved. Improving adherence to TB treatment is a strategy that seeks to address the last gap in the TB care cascade. However, there are various barriers that prevent this last but very important gap from being closed.

1.3 TB treatment success in South Africa

Treatment success for drug-sensitive Tuberculosis (DS-TB) is defined as either those PWTB who have been cured or who have completed six months of treatment. Cure is defined as confirmed smear negative or culture negative in the last month of treatment and on at least one previous occasion [4]. The WHO recommended target level for treatment success is 90% while that of South Africa remains concerning at 79% for new and relapse cases registered in 2021 [1]. The treatment success rate for those who are HIV positive with TB in 2021 stood at 79% while those previously treated with TB the treatment success rate was 60% [1]. A study done in SA by Naidoo et al, using the overall cases estimated in the country showed an overall treatment success rate of 54%, due to

the large proportion of patients never starting treatment [5]. Some reasons for the low treatment success rates could be due to death, loss to follow-up (LTFU), unevaluated treatment outcomes or treatment failure which is defined as , smear- or culture-positivity at the fifth month or later (or detection of multi-drug resistant TB at any point)[4] [6].

1.4 Barriers to completing TB treatment

Treatment failure among PWTB still persists as a result of treatment interruptions, although public health facilities have tried to implement strategies to improve adherence, such as the Directly Observed Treatment Short Course (DOTS) [7]. One study has shown that the possible reasons for non-adherence include: PWTB thinking that they are cured once they feel better; stigma; forgetting to take medication due to substance use; lack of support from friends and family; distance from clinics; lack of counselling; and poor relationships between PWTB and the healthcare workers (HCWs) [8]. Non-adherence to treatment increases the development of drug resistant TB [9] or a relapse in drug sensitive TB [10, 11] that are often difficult to treat requiring costly and toxic regimens creating further challenges to adherence [12].

1.5 Strategies to improve adherence to TB treatment

DOTs is highly resource intensive and is also not implemented at a national scale which limits its optimal use [7]. Two approaches have also been used for decades in SA to measure adherence: pill counts and self-report [13]. Pill count involves recording the number of pills distributed at each clinic visit and those remaining at the return visit while self-report requires the PWTB to state the missed doses to the HCW [13]. Despite the long existence of these approaches, a gap still remains in the accuracy of reporting adherence for reasons such as recall bias and social desirability [13, 14] which brings about the need for an improved method of accurately measuring adherence. Furthermore,

these approaches can only be conducted at a clinic or home visit hence they cannot monitor adherence in real time [13].

1.6 Use of technology to improve treatment adherence

One way of overcoming challenges to monitoring TB treatment adherence has been the introduction of innovative methods in the form of digital adherence technologies (DATs), which can be operated remotely and do not require in person clinic visits. Remote monitoring of treatment adherence was found to be useful during the COVID-19 pandemic where physical contact was not encouraged.

A DAT known as *99 DOTs* requires a PWTB to call a hidden phone number within the blister pack to indicate when a dose is taken [15]. 99 DOTS has the potential to reduce stigma due to its discreet nature. Still, it is limited in its ability to accurately report if a dose was taken, as the PWTB may dial the number without actually taking any medication [15, 16]. This challenge has been overcome by DATs methods like *Video DOT (VOT)* which allow HCWs to watch the PWTB taking treatment over video-conferencing hence it is considered a more accurate method to ensure that PWTB adheres to treatment [17]. In addition, VOT can be a source of support to those who lack family and friends to support them during their TB illness [18]. However, VOT requires a smartphone, data plan and sufficient bandwidth making it a less affordable method in low- and middle-income countries such as SA [17].

Ingestible sensors are another DAT method that may be more accurate in reporting adherence. Here a hidden microchip is placed within the TB pill that once swallowed will send a signal to an adherence monitor worn by the PWTB and then to a server monitored

by the HCW [15]. One limitation of ingestible sensors is that a PWTB may still forget to take their medication since this DAT does not come with reminders. A PWTB would then have to rely on an alternative DAT to remind them to take their medication making it a costly method.

An advantage of electronic pill boxes is that they could be less resource intensive by not requiring direct patient contact, and they allow for monitoring of dosing patterns of PWTB in real time from a central location. In addition, they remind PWTB to take their medication through the use of alarms and lights [15]. These reminders are especially useful for those PWTB who do not have adequate social support. Electronic pill boxes may allow for health system resources to be utilized more efficiently as only those who miss their doses would be targeted for follow-up and could be provided with specific care packages based on their needs i.e. differentiated care.

One disadvantage that can be anticipated with electronic pill boxes is that they are often bulky in size and have a loud alarm which may lead to unintentional disclosure of TB status thus interfering with adherence [19]. However, one study done in KwaZulu-Natal, SA showed that use of electronic pill boxes did not cause stigma or compromise confidentiality since pills were concealed [20]. Moreover, PWTB perceived HCWs as being supportive when their dose taking was remotely monitored [20]. Another disadvantage of electronic pill boxes is that the PWTB may open and close their monitor without swallowing their pills. Nonetheless, some studies have shown that there is a high correlation between pill box openings and treatment outcomes [19].

DAT methods each have their strengths and weaknesses and the selection of the appropriate DATs will depend on its technical capabilities and various other factors. These factors include how well the DAT can reduce stigma through addressing any privacy concerns, and how acceptable, usable and feasible it is by PWTB and HCW including the health system.

1.7 Use of and differentiated care models to improve treatment adherence

Differentiated care is a person-centered approach that adapts the services offered to the needs of the PWTB helping to shift utilization of resources to those who are in most need while also helping to reduce the resource demands on the health system [7, 9, 11]. Differentiated care models have been used in HIV treatment delivery with networks such as the HIV Coverage, Quality, and Impact Network (CQUIN) which have addressed challenges such as overcrowded facilities, overburdened staff and long waiting times in countries like Uganda, Swaziland, Mozambique and SA [15-18]. In HIV treatment delivery these service models are focused on those clients who are stable on antiretroviral treatment (ART) trying to enhance adherence to treatment by improving how ART is delivered [20]. These delivery models have mostly been used in high prevalence countries in sub-Saharan Africa providing sustainable access to ART and support services for the 37 million People Living with HIV (PLHIV) [21]. Differentiated care models have the potential to be adapted for use in TB treatment to differentiate the level of support needed for defined groups of PWTB based on their adherence patterns thus reducing the need for unnecessary clinic visits. This helps to reduce the burden on the health system while improving access to quality care [21]. Differentiated care models can also act as a way of reducing stigma and discrimination for clients when their context is considered [21].

1.8 Description of the TB MATE Trial

The TB MATE (TB Monitoring and Adherence Endpoints) trial was a pragmatic cluster randomised trial (CRT) conducted in South Africa between May 2019 to February 2022. The trial has been described in the CRT protocol published in the international journal *Trials* [22]. In the intervention arm, participants received medication monitors (Wisepill 1000 evriMED device) with reminders and differentiated care in response to real-time adherence data uploads, carried out from a central database.

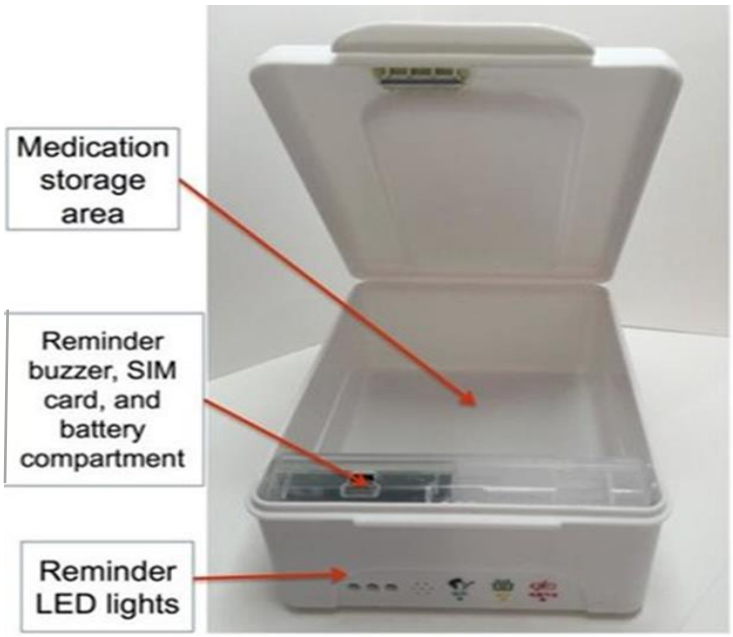

Figure 2: Wisepill 1000 evriMED device

The differentiated care was implemented in a progressive manner depending on the number of doses a PWTB misses. If one dose was missed, then an Short Message Service (SMS) reminder was sent to the PWTB. If a second or third dose was missed, then a research assistant would make a telephone call to the PWTB and once the fourth dose was missed then a home visit was made during which motivational counselling would take place. The project management staff downloaded a weekly report to calculate the number of missed doses for the week.

In the control arm, participants were provided with the medical device to measure adherence though they did not have reminders installed. Instead, pill box opening was recorded real-time in silent mode and the participants' adherence record was stored for analysis at the end of study. The routine standard of care (SoC) adherence practices such as pill count and self-reports carried on as usual.

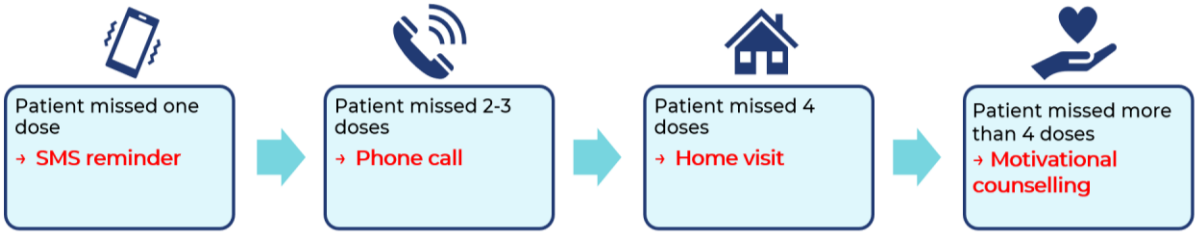

Figure 3: TB MATE Intervention. Differentiated Care Approach.

1.9 Justification for the research

Comprehensive evidence on the implications of DATs on a large scale is essential yet scarce. For a new technology to be successfully implemented, various components that are important include effectiveness, feasibility, acceptability, cost-effectiveness, PWTB costs, budget constraints, equity and policy buy-in. These components are important for policy making because effectiveness gives an indication of how well the intervention works to improve adherence to treatment while feasibility looks at the intervention fit within the existing health systems. Acceptability allows policy makers to understand the level of satisfaction that PWTB and providers have with the intervention whilst cost-effectiveness considers the costs of the intervention relative to the health outcomes achieved which in turn has an impact on the available national budget.

Effectiveness was measured by the parent study while this PhD study aimed to understand the feasibility, acceptability, cost-effectiveness and PWTB costs of the

adherence monitoring and support system. This evidence will guide policy decisions on which DAT to prioritize for successful large-scale implementation as improving adherence to TB treatment at a low cost will allow for scarce resources to be utilised efficiently. Furthermore, feasibility and acceptability are important considerations as they act as either barriers or facilitators to the uptake of the intervention to both stakeholders and PWTB.

1.10 Overall Aim

To determine the feasibility, acceptability and cost-effectiveness as elements that are necessary for the successful implementation and targeted policy buy-in of the adherence monitoring and support system being evaluated.

1.11 Specific Objectives

1. To describe the feasibility of implementing Wisepill evriMED device and differentiated care from a stakeholder perspective
2. To describe the acceptability of implementing Wisepill evriMED device and differentiated care from a PWTB perspective
3. To evaluate the cost-effectiveness of the intervention from a societal perspective

1.12 Conceptual Framework

Figure 4 is an adapted version of the Health Technology Assessment (HTA) model which illustrates the process of decision making used by policy makers prior to implementation of a new technology [52, 53]. The framework illustrates that evidence of effectiveness of the technology within a controlled setting needs to be supported by evidence on other considerations namely [1] feasibility; the relative ease of implementation and operation of the technology within existing health systems, technology infrastructure and supply chain [54, 2] acceptability; the relative satisfaction of PWTB with the differentiated model of

care [9, 3] efficiency; what are the implementation costs of the technology for the observed outcomes [9, 4] patient costs does the technology incur costs on the PWTB [9]. However, budget constraints and equity are two elements that will not be assessed during this PhD as they are beyond the scope that my PhD can cover within the timeframe.

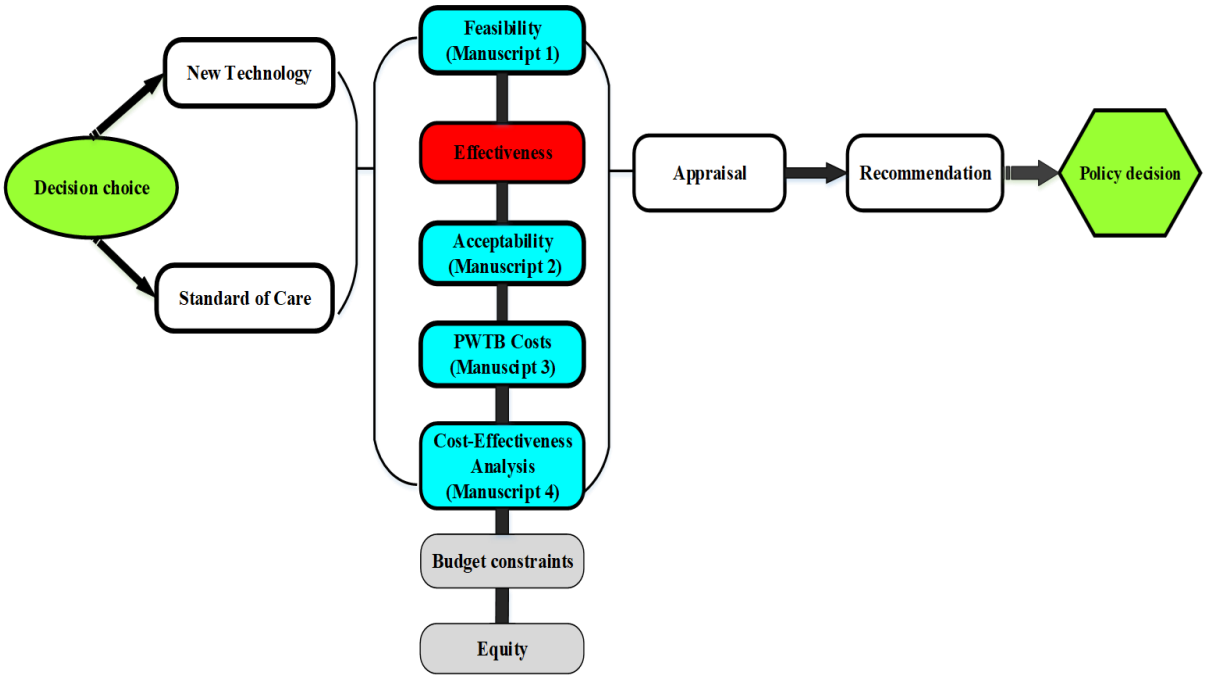

Figure 4: Health Technology Assessment (HTA) Framework (source - www.eupati.eu)

1.13 Gaps in evidence not addressed through this PhD

Budget constraints and *equity* are two elements that were not documented in the form of manuscripts generated from this PhD as they are beyond the scope that my study can cover within the limited timeframe. Both these elements are important considerations to guide decision making on which TB interventions should be prioritised by policy makers. I also conducted a theoretical assessment of equity (section 7.2) as it relates to DATs implementation. The only remaining gap is the budget impact analysis which will not be addressed through this PhD but through subsequent research.

1.14 Thesis structure

This PhD thesis is made up of seven chapters.

Chapter one gives a background to the study by highlighting the extent of the problem (TB incidence and mortality), why adherence to TB medication is important and ways that can be used to support PWTB to adhere and complete their treatment. The justification for my research as well as overall aim and specific objectives are presented in chapter one.

Chapter two delves into the available literature looking at the evidence surrounding effectiveness, cost-effectiveness, feasibility, and acceptability of DATs as important elements that can be used to guide decision making around the scale-up of a new technology.

Chapter three covers the methodology used in each of the manuscripts and highlights my role as a student.

Chapters four to six introduces each of the manuscripts in turn and presents the published manuscript or the final manuscript submitted to the journal.

Finally, chapter seven is a discussion of the main findings of the study in the context of the existing literature, a theoretical assessment of equity and the implications on policy.

CHAPTER 2: LITERATURE REVIEW

There is limited evidence on factors that may influence successful implementation of DATs such as effectiveness, cost-effectiveness, feasibility and acceptability. A literature search was conducted using PubMed database and google scholar. Search terms included 'digital adherence technologies', 'digital adherence technologies and TB and medication and pillbox'. I filtered for the following: abstract, free full text, books and documents, clinical trial, meta-analysis, randomized controlled trial, review and systematic review. From the literature search, most pilot studies on DATs use have been conducted in SA [15, 23-25]. Large studies on DATs have mostly been conducted outside SA like in China [26-28]. This literature review will attempt to look at all DATs in SA and mostly evidence on the medication monitor globally so as to give some context to understanding the pros and cons of medication monitors which is the focus of my PhD. A summary table of DATs evidence in SA is provided in table 3.

2.1 Evidence on Effectiveness of DATs

The following studies were found and reviewed on the effectiveness of DATs both in SA and globally.

Hüsler J et al. Evaluation of the On Cue Compliance Service Pilot: Testing the use of SMS reminders in the treatment of Tuberculosis in Cape Town, South Africa. 2005[22].

A pilot evaluation conducted in Cape Town SA by Hüsler et al assessed the **impact** of DATs through the use of **SMS reminders** to improve treatment completion and cure rates for PWTB [22]. The pilot study included 221 patient records and seven staff interviews and found that treatment completion and cure rates were similar in those PWTB using sms reminders and those using DOTs only [22]. Despite treatment adherence being an outcome of interest in this study, the researchers could not accurately measure if

adherence had improved or not but only showed that monitoring for treatment adherence was a problem where PWTB were not seen daily [22].

Liu X et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med. 2015;12(9):e1001876 [27].

Large studies on DATs have mostly been conducted outside SA like in China where 4,292 PWTB were enrolled between 1 June 2011 to 7 March 2012 into a large pragmatic cluster-randomized trial which measured **effectiveness** in four arms; using **text messaging reminders**, a **medication monitor**, combined or neither (controls), amongst DS-TB people [24]. Participants in all study arms were 18 years and older and they took their treatment from the medication monitor but the reminders to take treatment and for monthly clinic visits were only active in the medication monitor arm and the control arm [24]. The trial found that reminders from medication monitors improved medication adherence in PWTB, but text messaging reminders did not [24].

Liu X et al. Digital adherence technologies to improve tuberculosis treatment outcomes in China: a cluster-randomised superiority trial. The Lancet Global Health. 2023;11(5):e693-e703 [28].

A second cluster-randomized trial took place in China between 26 January 2017 and 3 April 2019 where 3,072 PWTB who were 18 years and older were enrolled [23, 25]. This trial measured **effectiveness** and **cost-effectiveness** using two study arms; the intervention arm where the PWTB received the **medication monitor** with reminders to take treatment daily, and the control arm where PWTB received a medication monitor with no reminders (in silent mode) [25]. This study found that the medication reminder

improved treatment adherence but however did not show an effect on poor treatment outcomes namely loss to follow-up and TB recurrence [25]. The results of the cost-effectiveness study are yet to be published. However, the health system in China is organised differently from SA which may have an influence on cost-effectiveness. In addition, both trials included adult participants aged 18 years and older and hence little is known about how the medication monitors would perform within the under 18 population involving children with TB and their parents/caregivers.

[19]

Wei X, Hicks JP, Zhang Z, Haldane V, Pasang P, Li L, et al. Effectiveness of a comprehensive package based on electronic medication monitors at improving treatment outcomes among tuberculosis patients in Tibet: a multicentre randomised controlled trial. Lancet. 2024;403(10430):913-23.

Recently a RCT was conducted in Tibet, China between November 17, 2018, and April 5, 2021 where 143 PWTB (DS-TB) 15 years and older in the intervention arm were offered a comprehensive package including medication monitors with reminders and a smartphone app which enabled text, audio, and video communication between patients and health-care providers [19]. The package also included a treatment supporter who was trained to support patients with using the electronic medication monitor and app [19]. In the control arm, 135 PWTB received medication monitors but with no reminders. They also did not receive the app or treatment supporter. The study found that the intervention package was effective in improving adherence (measured as missing 20% or more of planned doses in the treatment month) and five of the six treatment outcomes that were measured including treatment success (i.e. cured or treatment completed) [19].

2.2 Evidence on Cost-Effectiveness of DATs

Broomhead S et al. Retrospective return on investment analysis of an electronic treatment adherence device piloted in the Northern Cape Province. Telemed J E Health. 2012;18(1):24-31[24].

One pilot study done in the Northern Cape Province of SA on **digital pillboxes** assessed treatment outcomes and performed a **cost minimization analysis** (CMA) comparing the costs and health outcomes of the DOTS-SIMpill cohort with DOTS-only controls which showed improved treatment outcomes and cost savings [24]. However, this pilot study did not conduct a full cost-effectiveness which would have been a more rigorous method than a cost-minimization analysis. Cost savings were mostly evaluated by looking at the investment in pill boxes and no other resource inputs were considered when a comparison was made with the treatment costs averted. This could have potentially led to an overestimate of cost savings.

Hüsler J et al. Evaluation of the On Cue Compliance Service Pilot: Testing the use of SMS reminders in the treatment of Tuberculosis in Cape Town, South Africa. 2005 [25].

In the pilot study by Hüsler et al evaluating **SMS reminders** in Cape Town [25], the evaluators used a framework they referred to as "Real Access, Real Impact" which incorporated aspects of **cost** (and acceptability) of the technology. Cost analysis mainly took the form of patient costing where a limited scope of direct and indirect costs were included such as airtime, transport and lost wages. Provider costs were not evaluated.

Kafie et al. Cost and Cost-Effectiveness of Digital Technologies for Support of Tuberculosis Treatment Adherence: A Systematic Review.2024 [29]

A recent systematic review including literature from January 2000-April 2023 reviewed 29 studies which met the inclusion criteria out of 3,619 titles which were identified in the

search [29]. DATs included SMS reminders, phone-based technologies, digital pillboxes, ingestible sensors, and video observed treatment (VOT) and findings were largely from high-income countries[29]. VOT was the most extensively studied (16 studies) and was generally cost saving when compared to healthcare provider directly observed therapy (DOT)[29]. The authors concluded that DATs may be cost-saving or cost-effective compared to healthcare provider DOT [29]. Since these finding were mostly from high income countries, more data of higher quality are needed from low and middle income countries (LMICs)[29].

2.3 Evidence on Feasibility and Acceptability of DATs

The two large cluster randomised trials conducted in China did not evaluate acceptability and feasibility [27, 28]. The evidence on these aspects,until recently, has only been available through small pilot studies. The most recent trial to be conducted that examined the feasibility and acceptability of DATs is the ASCENT trial conducted in Ethiopia, The Phillipines, South Africa and Tanzania [30].

Tadesse AW et al. Feasibility and acceptability of the smart pillbox and medication label with differentiated care to support person-centered tuberculosis care among ASCENT trial participants - A multicountry study. Front Public Health. 2024;12:1327971 [30].

Use of the **smart pillbox** and **medication labels** were found to be **feasible** amongst PWTB (drug sensitive) across the four countries that were part of the ASCENT trial i.e. Ethiopia, The Phillipines, South Africa and Tanzania [30]. Medication labels containing a unique code were placed on their fixed dose blister-packaged TB medication [31]. When their daily dose was taken, participants messaged this code using a toll-free text, which automatically logged their daily dose to the web-based application [31].However, there were implementation challenges of using the medication labels and the smart pillbox such

as poor network, charging problems and phone credit which were more common in the Phillipines and hindered the DATs and differentiated care approach from working optimally. Another challenge cited was privacy concerns where PWTB did not want to be seen taking their treatment from the pill box as this may have led to disclosure of ones TB status causing stigma especially in the South African setting [30]. **Acceptability** of the DATs amongst PWTB was found to be high as measured using the COM-B model which examines capabilities, opportunities and motivations for behaviour change [30]. Lower mean scores for opportunities were influenced by fear of stigma related to using the pillbox and medication lables in public spaces [30].

Hüsler J et al. Evaluation of the On Cue Compliance Service Pilot : Testing the use of SMS reminders in the treatment of Tuberculosis in Cape Town, South Africa. 2005[25].

Feasibility of **SMS reminders** was not directly measured in the Cape Town pilot study although they looked at related aspects such as 'appropriateness of the technology within the context' and capacity issues. The findings were that SMS reminders are appropriate to complement DOTS in Cape Town clinics and beyond but certain barriers limit their usefulness such as tight clinic staff schedules and many staff members feel that they are over-worked [25]. Over the long-term, issues of privacy, data protection, and security have the potential to affect the widespread use of the technology in healthcare [25].

Acceptability of **SMS reminders** was found to be high with all 26 interviewees stating their support for the sms service and their ability to integrate it into their daily routines. Despite this, there were some privacy concerns with 20% of the participants interviewed being concerned that other people would see the sms from the clinic leading to unintentional disclosure of their TB status.

Bionghi N et al. Pilot evaluation of a second-generation electronic pill box for adherence to Bedaquiline and antiretroviral therapy in drug-resistant TB/HIV co-infected patients in KwaZulu-Natal, South Africa. BMC Infect Dis. 2018;18(1):171 [23].

Acceptability of DATs was also found to be high in a pilot study done in Kwa-Zulu Natal province of SA but only amongst 21 DR-TB and HIV co-infected people using an **electronic pill box device** [23]. In that study participants reported positive experiences with no concerns about stigma, confidentiality, or remote monitoring using the electronic pill box and expressed willingness to use the device during a full course of treatment [23]. The electronic pill box was found to be more accurate in terms of measuring adherence than the patient reported seven-day recall comparator. No other outcomes such as cost-effectiveness or feasibility were measured in this pilot study.

Sumari-de Boer M et al. Implementation and effectiveness of evriMED with short messages service (SMS) reminders and tailored feedback compared to standard care on adherence to treatment among tuberculosis patients in Kilimanjaro, Tanzania: proposal for a cluster randomized controlled trial. Trials. 2019;20(1):426 [32].

Another large study that evaluated the use of an **electronic pill box** amongst DS-TB people was conducted in Kilimanjaro, Tanzania where the intervention arm participants were given the evriMED pillbox while those in the control arm received DOTs as per standard of care [32]. This study was a cluster randomized trial which assessed **effectiveness**, **acceptability**, and **feasibility** among other aspects within an East African setting. The protocol was published in 2019 and we are awaiting the results of the study. However, even when the results of the study do get published, they may not be easily generalisable to SA given the differences in culture and infrastructural development between the two settings.

More recently there have been two published systematic reviews which have looked at health outcomes, costs and cost-effectiveness and acceptability of DATs [33, 34].

Ridho A et al. Digital Health Technologies to Improve Medication Adherence and Treatment Outcomes in Patients With Tuberculosis: Systematic Review of Randomized Controlled Trials. J Med Internet Res. 2022;24(2):e33062 [33].

In the first review published in 2022 by Ridho et al, the paper looked at the **effect** of DATs in improving medication adherence and clinical outcomes in patients with TB [33]. The review included 16 Randomised Controlled Trials (RCTs) and six types of DATs namely **video directly observed therapy (VDOT)** (n=3), **video-observed therapy (VOT)** (n=1), **ingestible sensors** (n=1), **phone call reminders** (n=1), **medication monitor boxes** (n=2) and **SMS text reminders** (n=8) [33]. The outcomes evaluated were treatment adherence, treatment completion and clinical outcomes as suggested by cure rate and smear conversion [33]. The review found that **treatment adherence** was increased in one small RCT (daily SMS reminders) done in Argentina using 18 PWTB (intervention arm) and 19 PWTB (control arm), while another RCT done in Taiwan on VDOT using 80 PWTB (intervention arm) and 160 PWTB (control arm) found no improvement in treatment adherence [27, 33, 35].

DATs were found to have a significant effect (odds ratios and relative risks ranging from 1.10 to 7.69) on **treatment completion** in four RCTs (VDOT, VOT, ingestible sensor, SMS reminder), where in two RCTs VDOT (n=112 intervention and 114 control) and VOT (n=50 intervention and 302 control) were studied in the UK and USA respectively and were found to be more effective than DOTs which was the standard of care [17, 36]. The other two RCTs on ingestible sensors (n= 41 intervention and 20 control) and SMS reminders (n=160 intervention and 190 control) were done in the USA and China

respectively and they also showed a positive effect on treatment completion [33, 37, 38]. However, three RCTs of VDOT [39-41] and three RCTs of SMS reminders [35, 42, 43] did not find significant effects for treatment completion [33]. Clinical outcomes (cure rate) showed that SMS reminders (odds ratio 2.47; 95% confidence interval 1.13-5.43) and phone calls (relative risk 1.30; 95% confidence interval 1.07-1.59) had a significant effect as seen in two RCTs [44, 45] while three RCTs found that SMS reminders did not have a significant effect on cure rate or smear conversion [33, 40, 42, 46].

Given the variable evidence across countries and across DATs, setting specific evidence on the effectiveness of DATs on a specific outcome such as treatment adherence and treatment outcomes, would be more reliable. Also, depending on the standard of care that is currently in place in a specific setting, the effect size of the DATs may vary as some traditional adherence measures may perform worse than others e.g. DOTs, self-report and pill count making transferability of results to another setting even more challenging.[47]

Oeser C et al. Digital approaches to reducing TB treatment loss to follow-up. Int J Tuberc Lung Dis. 2023;27(6):432-7 [34].

In the second review published in 2023 by Oser et al, the authors looked at **effectiveness**, **cost-effectiveness** and **acceptability** of adherence technologies [34]. Most studies were reported from an African country (n=10), followed by the United States (n=7) and China (n=6) [34]. The most common technologies included in the reviews were **VOT** (n=9), MERMs or **Medication Event Reminder Monitor** (n=6), **one or two-way text messaging** (n=5) and lastly **99DOTS** (n=2) [34]. There was heterogeneity in the effectiveness of the DATs where two-way SMS showed a 10% improvement in treatment success in a large RCT in Kenya [34, 47]. Likewise, MERM showed a 15% improvement

in treatment success in Peru and in Morocco where both increased adherence and treatment success were observed [34, 48, 49]. However, MERM did not show any improvement in treatment outcomes in a China trial [34, 50]. VOT showed improved adherence in studies conducted in United Kingdom [17], Moldova [51], United States [52], China [53, 54] and Taiwan [34, 55]. Similar to the previous systematic review, the RCTs show that DATs improve treatment adherence, but significant positive effects are often not observed with treatment outcomes.

The systematic review by Oeser et al on cost-effectiveness of DATs included six studies that showed DATs could be considered as being cost-effective over time and in high burden settings due to economies of scale [34]. Economies of scale are realised where capital costs are spread out over many PWTB over time and in high burden settings where TB incidence is higher. Acceptability of DATs with PWTB showed that DATs was acceptable depending on digital literacy, connectivity and how well the implementation of the DAT was modified to suit the target population e.g. preferred timing of communication [34].

Despite these studies, there are major limitations in understanding the effectiveness of using DATs within the South African setting. Minimal data exists on the performance of DATs in different geographical settings such as rural and urban, gender differences in the acceptability of DATs, experiences of HCWs using DATs at the public health facility and perspectives of different stakeholders on the feasibility of using DATS for the national TB program. Further investigation on the four elements; effectiveness, feasibility, acceptability, and cost-effectiveness of DATs is needed to inform the scale-up of technologies for TB adherence in resource-limited settings. My PhD will address three of these elements, feasibility, acceptability, and cost-effectiveness within the South African setting.

Table 1: Evidence of DATs in South Africa

Author, Year	Setting	DAT Tested	Aspect(s) assessed	Target Population	Findings	Limitations
Hüsler J et al, 2005[25]	Cape Town, SA	SMS reminders	Impact Feasibility Acceptability	New sputum smear-positive patients	Monitoring for treatment adherence is a problem where patients are not seen daily so study could not accurately measure if adherence had improved or not.	Cost-effectiveness was not assessed. Small study implemented in a limited area so findings cannot be generalized to all of South Africa.
Broomhead S et al, 2012 [24]	Northern Cape, SA	Digital pillboxes	TB treatment outcomes Cost per patient	New sputum smear-positive patients	Reduced cost per patient as a result of cost savings from improved treatment outcomes.	Acceptability and cost-effectiveness were not assessed.
Bionghi N et al, 2018 [23]	Kwa-Zulu Natal, SA	Electronic pill box	Accuracy Acceptability	Drug Resistant TB patients	Wise pill was more accurate (100%) compared to seven-day recall (0%) in detecting non-adherence. Patients reported positive experiences with electronic pill box and expressed willingness to use the device during a full course of treatment. No concerns about stigma, confidentiality, or remote monitoring.	Cost-effectiveness was not assessed.
Tadesse AW et al, 2024 [30]	Ethiopia Phillipines South Africa Tanzania	Smart pillbox Medication labels	Feasibility Acceptability	Drug-sensitive TB patients	Pillboxes and medication labels with differentiated care support were feasible to implement and acceptable	Perspectives of health care workers and other stakeholders were not assessed

CHAPTER 3: METHODS

3.1 Study setting

The cluster randomized trial (CRT) (and the PhD) was implemented in three districts of SA, Ekurhuleni (Gauteng Province), Cape Town Metro (Western Cape Province) and eThekwini district (KwaZulu-Natal Province) shown on the map below.

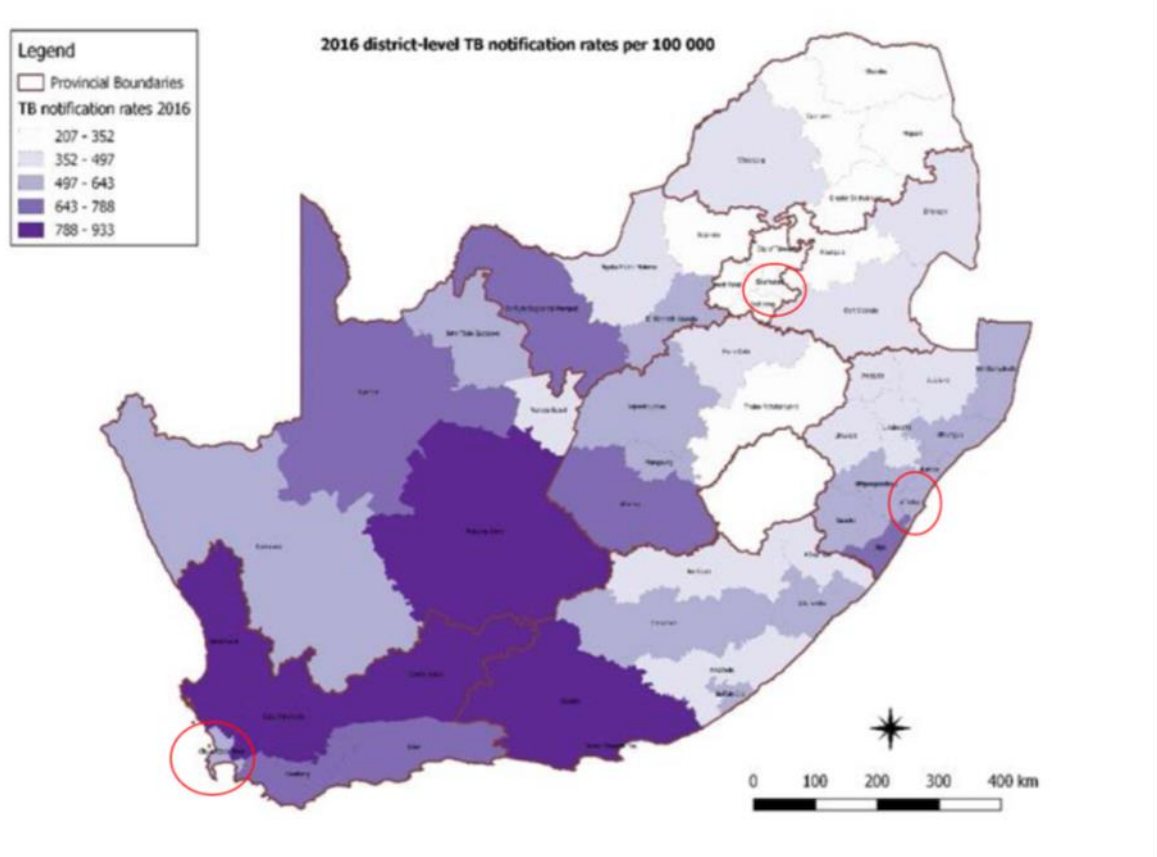

Figure 5: Map showing location of study sites in South Africa

3.2 Study population

The study population for the CRT consisted of adults and children above the age of 2 years who had drug-sensitive TB and initiated onto TB treatment within the last 14 days. The study population for my PhD included:

- TB healthcare providers (TB nurses and study staff) administering the TB MATE intervention to adults and children >2 years with drug-sensitive TB
- People with DS-TB 18 years and older accessing the intervention

3.3 Clinic selection

In each of the three districts, six primary health care (PHC) clinics, three in the intervention arm and three in the control arm, were randomly selected with a total of 18 clinics for the parent study. The PhD study was implemented in six clinics where we purposively selected one intervention and one control clinic per district to have a mix of clinics that are rural and urban, busy and quiet, large and small (based on the number of patients starting TB treatment per month) [22]. The 18 clinics were selected based on having at least 200 registrations in 2017 and were randomised to the two arms considering the location (urban vs rural), the total number of patients starting TB treatment per month, and treatment outcomes in the last 12 months. [22]. The clinics are shown in table 4:

Table 2: Clinic selection for the parent study and PhD

Province	**District**	**Intervention Clinic**	**Control Clinic**
Gauteng	Ekurhuleni	Daveyton Main	Dresser
		Tembisa Main	Goba
		Ramokonopi CHC	**Esangweni**
Western Cape	Cape Town Metro	**Gugulethu**	Mzamomhle
		Nyanga	**Phumlani**
		Tafelsig	Weltevreden Valley
KwaZulu Natal	eThekwini	Folweni	**Inanda C**
		Newtown A	KwaMakhutha
		Umlazi K	Phoenix

3.4 Study design

I implemented a cross-sectional study using a mixed methods approach to data collection for the PhD study.

3.5 Research methodology for objective 1

Objective 1: To describe the feasibility of implementing Wisepill evriMED device and differentiated care from a stakeholder perspective.

3.5.1 Sample size for the in-depth interviews on feasibility

The sample size included a total of 25 interviews which were categorised as follows:

- 7 stakeholders (Department of Health – National, Provincial and District levels)
- 18 healthcare workers (9 facility and 9 study staff)

At least two stakeholders in each of the three intervention districts were interviewed about the feasibility of the intervention. Key stakeholders per district were purposively selected from the Department of Health and invited to take part in the in-depth interviews based on their seniority, involvement in TB and with the intervention. One research assistant and one facility staff member from each of the nine intervention clinics were also invited for the feasibility interviews if they had been with the project for at least three months. The sample size was selected on the basis of obtaining a representative sample while also considering saturation where themes usually start to converge after 15 interviews.

3.5.2 Data collection for the feasibility of the adherence monitoring and support system

Feasibility was explored using a guide with various stakeholders from the Department of Health, research assistants and facility staff. The interviews were conducted in the study-approved languages namely English, IsiZulu, IsiXhosa, Sepedi and Afrikaans, audio recorded

with their consent and transcribed by a trained research assistant. No reimbursement was given.

3.5.3 Data analysis for the in-depth interviews on feasibility

Thematic analysis was used to analyse stakeholder interviews through deductive and inductive approaches [56, 57]. At least 10% of the transcripts were coded by two independent researchers to reduce bias and improve reliability [56]. A codebook of emerging themes was developed with discrepancies being resolved through discussion. Where there was no inter-rater agreement then the theme was dropped from the analysis [56]. Participant quotes were presented to illustrate the themes [58]. MAXQDA qualitative software was used for the coding process.

3.5.4 Role of the student

I conducted the stakeholder and PWTB interviews alongside qualitatively trained research assistants. I conducted a quality check of the transcriptions and/or translations. I performed the initial coding of the transcripts for objective 1 and my supervisor coded 10% of these and together we reviewed the codebook. I was the second coder for objective 2 alongside a master's student from the University of Witwatersrand who performed the initial coding under my supervision. I drafted the initial manuscript and revised subsequent versions as the first author.

3.6 Research methodology for objective 2

Objective 2: To describe the acceptability of implementing Wisepill evriMED device and differentiated care from a PWTB perspective.

3.6.1 Sample size for the in-depth interviews on acceptability

A total of 60 in-depth interviews on acceptability were planned with PWTB including at least 20 men and 20 women to ensure that views from both men and women were represented. The selection of PWTB was stratified by category of differentiated care. The sample size was selected based on saturation where themes usually start to converge after 15 interviews.

3.6.2 Data collection for the acceptability of the adherence monitoring and support system

Acceptability was explored qualitatively with participants using an in-depth interview guide. The interviews were conducted after implementing the adherence monitoring and support system to capture PWTB in all phases of treatment. Deductive themes included feelings and attitudes toward using the device ease of use of the device, perception and experience of receiving sms'es, home visits and motivational counselling, participants experience of stigma etc. The interviews were conducted in one of the study approved languages namely English, IsiZulu, IsiXhosa, Sepedi and Afrikaans, audio recorded with their consent and transcribed by a trained research assistant.

3.6.3 Data analysis for the in-depth interviews on acceptability

Data analysis for the acceptability interviews followed the same approach as for the feasibility interviews detailed in section 3.5.3 above.

3.6.4 Role of the student

My role remained the same as in objective 1 above on feasibility.

3.7 Research methodology for objective 3

Objective 3: To evaluate the cost-effectiveness of the intervention from a societal perspective

This objective was conducted from a societal perspective where the data was obtained from the PWTB costs, health system costs and the parent trial treatment outcomes data.

3.7.1 Sample size for the PWTB costing interviews

At baseline, all participants at each of the 18 clinics were interviewed for their demographic information. At their 2-month and 6-month visits, a sub-set of the study population were selected to participate in the PWTB costing interview. At each clinic, I used simple random sampling to select 55 participants in each treatment phase.

3.7.2 Data collection for PWTB costs

The interviews were conducted at the month 2 visit (end of intensive phase) so as to capture the pre-treatment costs and around the 6-month follow-up visit (end of continuation phase) by use of a questionnaire [59]. A sub-sample, randomly selected, was used since interviewing fewer participants' would allow us to spend more time and counter some of the recall bias [60]. The questionnaire was adapted from the REACH (Researching Equity in Access to Healthcare) project that was a multi-centre study that estimated the true costs of health care utilization for PWTB receiving 'free' HIV/TB care and treatment in rural KwaZulu-Natal [61] and the World Health Organisation TB Patient Cost Survey [59]. The questionnaire was piloted on a few participants before the official data collection began. All data was entered into a database created in REDCap.

3.7.3 Data analysis of PWTB costs

Data were exported from REDCap into STATA (version 14, StataCorp LP, College Station, Texas) for analysis. Economic costs that were assessed included direct and indirect costs related to the PWTB. . Both direct and indirect costs were summarised using means and standard deviations for normally distributed data and for skewed data medians and interquartile ranges were reported.

3.7.4 Sample size for time and motion studies

The sample size was selected based on convenience where the target was at least 10 observations of the TB nurse and the implementing research assistant for the initiation/enrolment visit and at each of the 6 monthly visits. Another 10 observations were planned in each of the three intervention sites for home visits.

3.7.5 Data collection for health systems costs

A micro-costing method using a bottom-up activity-based costing approach was used to measure health systems costs at both intervention and control clinics. This involved conducting time and motion studies at the clinic-level where the duration in minutes of all services rendered during the visit were recorded. The quantities of equipment and supplies used were also observed. Overhead costs for those resources that are shared were estimated. Time spent on staff training was obtained through interviews with the project managers. Financial records were reviewed for data on salaries of the implementing project staff and clinic staff involved in the intervention.

3.7.6 Data analysis for health systems costs and societal costs

Any time spent on research activities such as enrolling participants into the trial, were excluded during the analysis stage. Total costs were calculated by multiplying the intervention unit cost per PWTB at each visit and the number of PWTB who were seen in both trial arms. Health systems costs were analysed and reported according to internationally accepted standards as cost per PWTB receiving the Wisepill evriMED device. Societal costs (which include both patient and health systems costs) were reported as cost per adherent PWTB (with >80% adherence to DS-TB treatment).

3.7.7 Role of the student

Trained research assistants collected the data. I designed the time and motion forms, developed the PWTB questionnaire, trained the research assistants, managed the data collection and entry, quality-checked the data and analyzed the societal costs. With the support of my supervisors, I drafted the initial manuscript and revised subsequent versions as the first author.

CHAPTER 4: THE FEASIBILITY OF IMPLEMENTING WISEPILL EVRIMED DEVICE AND DIFFERENTIATED CARE FROM A STAKEHOLDER PERSPECTIVE

4.1 Introduction

This was a qualitative paper that explored themes such as feasibility of implementing the Wisepill evriMED device and differentiated model of care, and the system level challenges of delivering, sustaining and integrating the intervention into the existing TB programme. The qualitative study has shown that Wisepill evriMED device and the differentiated model of care is feasible to implement within the existing health system. Providers felt the intervention could be easily integrated into the health system and it would assist them in monitoring and supporting adherence to treatment for PWTB and also those with other chronic conditions. More details can be found within the paper.

4.2 Paper 1: Qualitative study exploring the feasibility of using medication monitors and a differentiated care approach to support adherence among people receiving TB treatment in South Africa

BMJ Open

Qualitative study exploring the feasibility of using medication monitors and a differentiated care approach to support adherence among people receiving TB treatment in South Africa

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ABSTRACT

Objectives The tuberculosis (TB) MATE study evaluated whether a differentiated care approach (DCA) based on tablet-taking data from Wisepill evriMED digital adherence technology could improve TB treatment adherence. The DCA entailed a stepwise increase in adherence support starting from short message service (SMS) to phone calls, followed by home visits and motivational counselling. We explored feasibility of this approach with providers in implementing clinics.

Design Between June 2020 and February 2021, in-depth interviews were conducted in the provider's preferred language, audiorecorded, transcribed verbatim and translated. The interview guide included three categories: feasibility, system-level challenges and sustainability of the intervention. We assessed saturation and used thematic analysis.

Setting Primary healthcare clinics in three provinces of South Africa.

Participants We conducted 25 interviews with 18 staff and 7 stakeholders.

Results Three major themes emerged: First, providers were supportive of the intervention being integrated into the TB programme and were eager to be trained on the device as it helped to monitor treatment adherence. Second, there were challenges in the adoption system such as shortage of human resources which could serve as a barrier to information provision once the intervention is scaled up. Healthcare workers reported that some patients received incorrect SMS's due to delays in the system that contributed to distrust. Third, DCA was considered as a key aspect of the intervention by some staff and stakeholders since it allowed for support based on individual needs.

Conclusions It was feasible to monitor TB treatment adherence using the evriMED device and DCA. To ensure successful scale-up of the adherence support system, emphasis will need to be placed on ensuring that the device and the network operate optimally and continued support on adhering to treatment which will enable people with TB to take ownership of their treatment journey and help overcome TB-related stigma.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We conducted the study in three provinces with different health service characteristics, tuberculosis epidemiology and population characteristics, which allowed us to understand feasibility of implementation from a broader perspective.
⇒ Another strength was that the study was done in a routine setting with limited resources and without the use of incentives to providers to increase uptake.
⇒ One limitation is that some of the interviews were conducted by a member of the study management team, although this was limited to senior stakeholders who were unlikely to feel reluctant to freely express their views and to withhold some of their opinions.

Trial registration number Pan African Trial Registry PACTR201902681157721.

INTRODUCTION

Globally, the treatment success rate for new and relapse drug-sensitive tuberculosis (TB) is 86% while in South Africa (SA) this is much lower at 79%.[1] Among those who are HIV positive with TB, the treatment success rate is 78% and 67% for those previously treated with TB.[1] Treatment failure is often a result of non-adherence to treatment, lost to follow-up or unevaluated outcomes.[2] Typical reasons that people with TB (PWTB) might not adhere to treatment include false perceptions of being cured once they feel better, stigma, forgetfulness, lack of social network support and poor user experience of accessing care at clinics.[3] Traditional methods such as Directly Observed Treatment Short course (DOTs), pill counts and self-report have limitations and have not been shown to

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improve treatment adherence in PWTB, especially where DOTs programmes are not designed and implemented appropriately.[4–6] The effectiveness of DOTs is influenced by higher DOTs coverage where cure rates have been found to be higher among those DOTs supporters with fewer patients allocated to them.[5] Digital adherence technology (DAT) including medication monitors may overcome challenges to monitoring TB treatment adherence through remotely documenting dosing patterns of PWTB.[7]

Both globally and in SA, there is limited information on the value of DATs in TB treatment. A study done in KwaZulu-Natal SA among drug resistant TB-HIV coinfected inpatients using an older version of the Wisepill device, the RT2000 3G, showed that feasibility challenges for digital pillboxes may include battery failure, device malfunction and problems related to cellular networks.[8] Previous studies have found that other DAT such as short message service (SMS) reminders for TB treatment were insufficient to improve treatment adherence alone. Barriers included frequent changing of phone numbers and uncertainty whether patients were taking their tablets immediately after they received the SMS or not.[9] Another study done in Uganda for HIV treatment showed that challenges for cellphone-based strategies included: use of shared cell phones, technical failures preventing receipt of SMS texts, electricity outages and changing phone numbers.[10 11] Another DAT known as 99 DOTs also has the potential to improve treatment adherence as the PWTB is required to call a hidden phone number within the blister pack so as to indicate when a dose was taken.[10] However, 99 DOTS is limited in its ability to accurately report if a dose was taken since the PWTB may dial the number without actually taking any medication.[10 12] This challenge has been overcome by DATs methods like Video DOT (VOT) which allow heathcare workers (HCWs) to watch the PWTB taking treatment over video conferencing, hence it is considered a more accurate method to ensure that PWTB adhere to treatment.[13] In addition, VOT can be a source of support to those who lack family and friends to support them during their TB illness.[14] However, VOT requires a smartphone, data plan and sufficient bandwidth making it a less affordable method in low-income and middle-income countries such as SA.[13]

Most DATs have focused on monitoring adherence and few studies have used DATs to differentiate between those patients who are struggling and need individual support, and those who are doing well. Given this gap in knowledge, we evaluated the feasibility of using the Wisepill evriMED DAT to monitor TB treatment adherence while using a differentiated care approach (DCA) with a stepwise increase in adherence support for PWTB in SA.

METHODS

Study design and study setting

This qualitative study was embedded within a cluster-randomised trial (CRT) that took place in six clinics in each of three provinces of SA: Gauteng (Ekurhuleni district); Western Cape (Klipfontein and Mitchell's Plain districts) and Kwa-Zulu Natal (eThekwini district), the details of which have been published elsewhere.[15] In the intervention arm of the CRT, PWTB received medication monitors with reminders triggering DCA in response to adherence data uploads, carried out from a central database.[15] The DCA was implemented in a progressive manner depending on the number of doses a participant missed.[15] If one dose was missed, then an SMS reminder was sent to the participant.[15] If a second or third dose was missed, then study staff would make a telephone call to the participant and once the fourth dose was missed then a home visit was conducted during which motivational counselling took place.[15] We describe the feasibility of implementing Wisepill evriMED device and differentiated care from a stakeholder perspective.

Site selection

There were a total of nine intervention clinics, three in each province. Clinics were selected based on location, HIV prevalence and numbers of patients starting TB treatment per month.[15]

Study population

The study population consisted of seven purposively selected stakeholders from the Department of Health: one national, one provincial and five district-level representatives, who worked closely with the facilities using the electronic device (Wisepill evriMED DAT). From each intervention facility, we interviewed one facility staff (government employee) and one study staff member. All study staff worked on the project for at least 3 months. Facility staff-initiated patients on TB treatment and monitored patients for their scheduled monthly follow-up visits while study staff offered PWTB the device, followed-up on those who had missed doses and provided motivational and adherence counselling.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Conceptual framework and themes explored

Using the feasibility framework suggested by Bowen *et al*,[16] we developed an in depth interview (IDI) guide (online supplemental appendix 1) that covered the following topics; (1) the relative ease of implementation and operation of the technology within existing health systems, technology infrastructure and supply chain and (2) system level challenges of delivering, sustaining and integrating the intervention into the existing TB programme. We used the framework on the 'Integration and sustainability of interventions into health systems'[17] to organise the data.

Data collection

We conducted a total of 25 IDIs. The sample was representative of providers involved in the intervention while

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also considering saturation where themes usually start to converge after 15 interviews. The IDI guide (Appendix I) was piloted with one stakeholder, two facility and one study staff between January and February 2020. The probing questions were adapted after the pilot. These interviews were conducted face to face, and the data were included in the analysis. Data collection continued between June 2020 and January 2021 with each interview lasting between 45 and 90 min. The interviews were all conducted in the providers preferred language by a female PhD student (RM) and a female study coordinator who was a PhD student with qualitative experience (VM). Both researchers established a prior relationship with the providers enabling them to understand the reasons for the study. The interviews were digitally recorded with the providers consent and transcribed verbatim by trained research assistants (masters students). The transcripts were not returned to the providers for comment or correction. Due to the impact of COVID-19 and the national lockdown that took place, these interviews were conducted virtually over Microsoft Teams. No one else was present in the interviews besides the providers and the researchers and field notes were made during the interviews. Saturation was assessed during data collection through asking the same question in different ways and reviewing a sample of the recordings until no new information was obtainable. No repeat interviews were carried out.

Data analysis

Thematic analysis was used with deductive and inductive approaches.[18 19] At least 10% of the transcripts were coded inductively by two independent researchers so as to reduce bias and improve reliability.[18] A codebook of emerging themes was developed, guided by the framework on the 'Integration and sustainability of interventions into health systems',[17] with discrepancies being resolved through discussion. Where there was no inter-rater agreement, the theme was dropped.[18] The final codebook was used to code the remaining transcripts and any new codes that emerged were also included in this codebook. MAXQDA qualitative software was used for the coding process. We highlight the major themes (overarching theme) and subthemes (specific themes) that emerged and use supportive direct quotations from providers. Providers did not provide feedback on the findings.

RESULTS

We conducted 25 interviews in total with 18 staff (9 facility staff and 9 study staff) and 7 stakeholders (1 national,1 provincial and 5 at district level) across 3 provinces. Majority of the providers (23 out of 25) were female. None of the approached providers declined to participate. Major themes included (1) Providers were supportive of the intervention, (2) Intervention challenges within the adoption system and broad context, and (3) Ensuring intervention sustainability through constant training of staff and education of PWTB

Major theme 1: providers were supportive of the intervention

There was buy-in from staff who felt involved and were supportive of the intervention. Stakeholders were also very supportive of the intervention despite their limited involvement.

> … to me it was a very good idea and it was working very well … it improved our cure rate because we had a lot of patients who were defaulting and who and to be referred to the hospital because they developed multi, MDR. So since we had …this intervention, at least we had less patients who developed multi-drug resistance. - FFS_019_7

> …I think…it's magnificent. I think it's… a tool box, it's really a way for us to see what's really happening at the point of … TB treatment, where the patient take… the medication when they open the box. So I think it's really innovation that can be used. … I think it also is a reminder for the patient. You know? That … "I need to take my medication". And it's a way to …to ensure the quality of the programme, that patients are adhering to the … medication…I think it is a critical intervention. – FDS_WC_008 (District level)

Both facility and study staff found the device easy to learn and facility staff who had received a briefing on the study were eager to receive the complete training to support the study staff.

> Because sometimes she (referring to study staff) [might not be here and it happens that she's not here, either she is sick or she's gone on holiday for December. She says: "…we can show you and then you do this things when we are not here". I said: "… it will be easy… As long as you show us, we can do that device. - FFS_762_003

The staff described the activities of the intervention such as issuing devices, phone calls and making home visits as being well integrated into the TB programme. Providers had strong support for the device for two main reasons that we classified as subthemes in our analysis:

Subtheme 1: device as a useful reminder and early notification tool

Most providers found the alarm that was fitted on the device to be a useful reminder to patients to take their treatment on time and to attend their clinic visits. The device also alerted providers to PWTB who were not using the device and not taking treatment.

> I feel like it assists with the real time monitoring because now if you check on the system, you would be able to check instead of waiting like someone waiting for their appointment that is months after, you can actually check now on the system that this person there's no activity, let me call and you would actually find that the person has died or maybe the person has—is in hospital is admitted.- FSS_762_006

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So, it will help us because …sometimes we notice the other patient…didn't take their medication and start to recall all of them and then the other just default … With the box, someone is getting … a notification that this person is not taking her treatment… - FFS_524_006

However, some staff distrusted that opening of the device meant that PWTB took their pills.

…some patients do that when they open the pill box and … show an adherence of 100%, but still they… have not been taking their medications. So we would try to motivate them, counsel them, explain the disadvantages of not of them not taking the medication. - FSS_519_001

I think because you know patients always find a way to find loopholes within the health system, so at some point they will understand that you're recording the opening and the closing of the box not necessarily them actively taking the medications. So they can easily open and close the box without really taking the medication. - FDS_GP_008 (District level)

Subtheme 2: DCA allows for patient-centred care

Staff mentioned that they found DCA to be a positive and unique aspect of our intervention.

So, you are no longer administering intervention for one. You sort of trying to be specific …to a person and offer them care in their in their specific sort of situations. So, I think that is a positive thing because you don't assume everyone is the same. You don't assume everyone's situation is the same. You understand that you are dealing with … individuals. That's … what I think is positive about this differentiated model of care. - MSS_732_005

… yah, I think I think the differentiated model of care … is a very positive thing, that it works to an extent because it's not a blanket approach. You don't, you don't think of every patient as the same…you sort of attend to each person in their context and … try to understand what they are going through. - MSS_732_005

The staff also felt that the counselling they provided as part of the DCA helped them to understand their patients' reasons for not taking their treatment thus allowing them to manage them better as they supported them on their treatment journey.

This whole approach I feel like it's a great initiative because it assists in managing the patient—like fully. Like if I can say wholly, not just managing the patient, taking the medication. You could also like… with the counselling you actually find that the problem is that the participant is facing beyond treatment intake.- FSS_762_006

Phone calls to PWTB allowed for clarification on any issues that may not have been clear to the patient while at the clinic.

…he didn't understand but when I called him and I was speaking to him over the phone to understand how they're taking the treatment, I find that … yeah there was mistake … one of the best things about this intervention because some of them are able to even call me up, I don't always now have to call patients. - MSS_732_005

Home visits allowed the staff to have better interaction with their patients and to build trust with them making them feel like someone cares about them.

It's not bad. It's nice to do home visits. It's whereby … you contact with the patients, know each other … where the patient has got the problem, it's with the … problem with the box or she wanted to ask me something that she forget to ask at the clinic. - FSS_522_002

… I think the participant at least get that thing when you do home visits, or you phone them when they are not taking the treatment they feel as if they are cared of, someone is care is cared for me when I am not taking the treatment because I would get a call, or I will get a home visit'- FSS_524_003

Some providers described DCA as more of a journey of supporting the patients and helping build trust between the staff and the PWTB.

… that is really good part of the intervention. I think it … continue to build that trust…And that support for the patients … so I- I think that was impressive. - FDS_WC_008 (District level)

I thought it was only about the box… it's more than them just using the box. It's their treatment journey and being supported to adhere to the treatment and get healed from the TB. - FSS_762_006

Major theme 2: intervention challenges within the adoption system and broad context of SA

Some staff felt that the trust they built with the PWTB could be threatened by human resource (HR) shortages and a dedicated cadre was needed to ensure successful implementation.

However, when we find at once the research study stop and we over onto implementation, … the constraints is always HR resources and at the operational level, if that initial education isn't framed correctly. There could be a misunderstanding about the purpose of the box. - FDS_WCR_008 (District level)

Challenges that were encountered with the device or the network resulted in delays in the system updating that the box was opened which staff felt created trust issues between them and the participant.

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Now it's creating a trust issue between you and the patient, because you phoning regarding treatment that was not taken because … Wisepill says treatment was not taken, while the patient on the other side did take the medication.- FSS_516_002

HCWs reported that some patients received incorrect SMS's due to delays in the system.

Especially when it has been a weekend and then they will not … send out the data of… the weekend like … if there were any missed or any … intakes. Sometimes they will show that they missed the weekend and they did not take the medication, but in three days down the line… the correct information will show. That's where we will see that there were no missed doses.- FSS_519_001

Staff also felt that that the device would not work for some group of patients such as those who abuse substances.

The patient that are on substance abuse, yoh! You know, when they come here, they are ok. At a later stage, once they've started treatment, you realise that this patient is using substances…With those patients, they the device- ya. It's not good. Won't- won't work. Won't- won't help. - FFS_762_003

He took the evriMED box device and the TB meds. That was the last time we saw him on the clinic. He run away from home apparently. He was on drugs. But then…he is back. He's here in the TB room. He's got TB again. So I was asking him the other day: "are you still interested in joining this study?". And he was like: "you know what I did with the first box? I sold it. - FSS_521_001

Subtheme 1: Provider perceptions of stigma related to use of the evriMED device and DCA

Staff perceived that some of the features of the box such as the alarm and the size of the box may have been a concern to some PWTB in trying to conceal their TB status so they would opt to leave their devices behind when travelling on holiday or going to work for fear of disclosure of their TB status.

The thing that is common, especially in December … an example is person supposed to take it at 8, they take it at 8 but they not taking it at 8 from the box… I think they went for holidays … This person is taking treatment and the putting it… in a purse. Whereby you'll take in the morning without this alarm ringing.'- MSS_019_002

So some will come to us and say: "what if the pill box doesn't make so much noise? It will be easier for me to carry around—or if it was a bit … smaller, then it will be easier for me to carry it. But now it's big, I don't want … people seeing me like with this pill box in the taxi or at work.- FSS_519_001

I haven't disclosed to my partner that I'm on TB medication and imagine if I had to carry this box and the box would be ringing in the morning and it would cause unnecessary fights. - FSS_762_006

Providers perceived that stigma was more of an issue outside the PWTB household as often they would not disclose their TB status to members outside their homes.

So, I noticed that it's comfortable for them to use this box when they are at home with the people that actually know what is going on with them but when they are going to other people that are not aware that they are sick or anything, it seems as if they don't want to carry the boxes. - FSS_762_006

Staff perceived that stigma related to DCA existed in the community and some of them witnessed the PWTB fear of being stigmatised when conducting home visits. PWTB would often ask staff not to wear their uniforms when they visit their homes.

Uhm they hate it when we wear our TB MATE t-shirts, because they are saying: "due to stigma". When we go visit their homes, we must not wear something that will be written 'TB' or 'HIV'. So we wear our normal clothes…- FSS_521_001

Then I took off my jacket, and then the participant saw that TB MATE on my t-shirt. And then the patient told me that I must wear my jacket because what if someone walks in and sees the TB MATE on my t-shirt. So I wasn't aware that the participant didn't disclose… She told me that she's got fear that—because she will be judged because she was drinking alcohol a lot. But now she's got TB. They will say she must go and stay in the back room.- FSS_521_001

Staff perceived that some stigma could have been internalised and not actually experienced by PWTB.

It's their thoughts because the person would feel like it did not want to be seen carrying the box. Because people will think- so he sees all their thoughts. It's not something that really happened.- FFS_732_001

But in the clinic, there wasn't really anything that contributed to the stigma but maybe with now giving the pill box… some of the patients would say that maybe it's gonna show. Maybe with their ARV's they could take it in private. Now we have them having this pill box that is gonna ring even, that is gonna beep and remind them to take treatment… - FSS_732_005

Major theme 3: ensuring intervention sustainability through constant training of staff and education of PWTB

Education on the intervention emerged as one of the major themes that stakeholders and staff placed emphasis on as a means of managing their patients in a holistic way leading to successful treatment outcomes. Education and training should emphasise the importance of adhering to treatment and should be strengthened at various levels—with the PWTB themselves, those who would be involved

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in implementation such as community health workers and also to the community at large.

> My experience was that as the community we need to need to educate the community the importance of complying to medication…we need to educate and educate and educate.- FFS_019_007

> But I definitely think it's… strengthening that interface between the patient and the staff… it's an important interface. And- and of course that too- the 'how' of- of the contact, if it is about 'why you didn't- why you aren't taking your treatment' rather than saying 'how are you doing'- you know- 'are you ok', uhm 'how can I help you'. When we start off with those different conversations, it can lead to different outcomes. - FDS_WC_008 (District level)

The staff felt that constant education and reinforcement would ultimately lead to behaviour change and treatment adherence.

> I think the intervention even though we are the one offering the intervention but we sort of gave patients the power to understand the… reasons why they are taking treatment, why is it important for them to…adhere to the treatment…we were actually able to make patients to take their treatment journey into their own hands … it's almost like we were empowering patients…- MSS_732_005

DISCUSSION

Using the Wisepill evriMED device to support adherence to TB treatment appears to be a feasible option in SA. Providers were supportive of the evriMED device and the DCA, as they felt it had a positive impact on the TB patient's programme. Stakeholders were supportive despite their involvement being limited to approval of the study and providing oversight of the TB programme.

This study has shown that DATs is an innovative approach that might improve the management of PWTB by allowing individual differentiated support. Early notification of missed doses from the device allowed staff to intervene through SMS messaging and phone calls, thus reducing the need for a home visit. This freed up time for staff to focus on other duties. These findings are similar to other studies where differentiated care models used in HIV treatment delivery have addressed challenges such as overcrowded facilities, overburdened staff and long waiting times in countries like Uganda, Swaziland, Mozambique and SA.[7 20–22]

Staff noted that the differentiated care allowed a journey of educating and supporting PWTB. Through adherence and motivational counselling, staff empowered patients to understand the importance of adhering to treatment and to empower them to take their treatment journey into their own hands. For scale-up, the real time monitoring feature of the device is important so that the correct individuals are promptly identified for further support before they become lost to follow-up. This also allows for the efficient utilisation of resources to those in most need, as seen in various studies.[6 23 24] More attention should also be given to relationship training as the sustainability of the intervention depends on a sound provider–patient relationship. Correct framing of the intervention as a support tool would also help ensure that the intervention is well perceived once scaled up. Training needs to be constant and not once-off to reinforce their understanding of the intervention. In a routine TB programme setting, training of healthcare providers could be conducted by subdistrict co-ordinators since they visit facilities on a regular basis for monitoring purposes.

Some challenges with the technology were cited such as alarm malfunction, incorrectly sent SMS's and short battery lifespan. These challenges created distrust from PWTB, and the device would, therefore, need to be of the highest quality to ensure sustainability of the intervention. A systematic review of DAT for the management of TB therapy found similar feasibility challenges remain in low-income and middle-income settings.[10] Once the intervention is scaled up, the shortage of HR could serve as a barrier to ensuring that providers receive the correct information. For successful scale-up, some staff recommended that a dedicated cadre should be in place to follow up PWTB to ensure that they understand the importance of taking treatment. However, since the support system had reduced the need for home visits and follow-up calls, the current TB cadres, clerical staff and community-based teams were also seen as being sufficient. Despite any challenges experienced within the adoption system and broad context, the staff were all very supportive of the intervention and even recommended that it should be used for all TB and chronic patients as well as in other facilities.

Fear of stigma and the disclosure of one's TB status has the potential to act as a barrier to scale up and sustainability of the intervention, if not well addressed. Stigma and fear of disclosure resulting in lower acceptance of DAT technologies among multidrug resistant TB patients have also been reported in India,[25] with improvements recommended on the design. Disease-related stigma may be more difficult to address, and screening should be used to identify upfront those patients whom stigma and fear of disclosure may limit the use of the MERM.[25]

A limitation of the study was that interviews had to be conducted virtually on Microsoft teams, due to the COVID-19 pandemic and to allow for effective social distancing for both the researchers and the study providers. This new mode of conducting interviews had setbacks such as network and connectivity challenges which interrupted the flow of some of the interviews. The interviewers mitigated this challenge through reiterating what the participant had said to ensure that the correct message had been captured. Through the consenting process, we were able to ensure confidentiality and that

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the participant was relaxed. A second limitation is that some of the interviews were conducted by a member of the study management team, although this was limited to senior stakeholders who were unlikely to feel reluctant to freely express their views and to withhold some of their opinions. Patients were not included in this study which is a limitation since their views would have added a broader understanding on feasibility. We conducted the study in three provinces with different health service characteristics, TB epidemiology and population characteristics which allowed us to understand feasibility of implementation from a broader perspective. Another strength was that the study was done in a routine setting with limited resources and without the use of incentives to providers to increase uptake.

CONCLUSION

DAT such as medication monitors has a huge potential to improve TB treatment adherence. However, to ensure successful scale-up and sustainability of the intervention, the DCA should be used as a platform to constantly educate PWTB and the community at large on TB and the importance of adhering to treatment since technology on its own will not solve treatment adherence issues especially those related to stigma and lack of support. Sound communication between PWTB and providers serves as a key tool to improving treatment outcomes thus more attention should be given to relationship training to ensure that the provider–patient relationships provide the necessary support to those who need it most.

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CHAPTER 5: THE ACCEPTABILITY OF IMPLEMENTING WISEPILL EVRIMED DEVICE AND DIFFERENTIATED CARE FROM A PWTB PERSPECTIVE

5.1 Introduction

This was a qualitative paper that explored the PWTBs acceptability of the Wisepill evriMED device and the differentiated model of care. This paper has shown that Wisepill evriMED device and the differentiated model of care is acceptable to PWTB as it acts as a reminder to take medication especially for those who do not have family support. More details can be found within the paper.

5.2 Paper 2: Acceptability of using the medication monitor and experience of a differentiated care approach for TB treatment adherence among people living with TB in South Africa

PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Acceptability of using the medication monitor and experience of a differentiated care approach for TB treatment adherence among people living with TB in South Africa

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Abstract

Background

The introduction of digital adherence technologies (DATs) such as medication monitors in tuberculosis (TB) programmes supports treatment adherence among people with tuberculosis (PWTB). We evaluated the acceptability of using medication monitors (Wisepill evriMED) prompting a stepwise differentiated care approach (DCA), involving short message service (SMS), phone calls, home visits and motivational counselling, among PWTB in South Africa.

Methods

We conducted 62 in-depth interviews with participants in local languages across three provinces (January—October 2020), purposively selected by treatment month, adherence history and gender. Interviews were audio recorded, transcribed verbatim and translated. Using a deductive approach and the Theoretical Framework for Acceptability (TFA), we explored acceptability across the sample attributes.

Results

PWTB across adherence histories showed a positive attitude to using the evriMED device and receiving the DCA support. PWTB described the SMS reminders and phone calls as effective reminders, though home visits were less acceptable, due to perceived stigma. Despite willingness to participate in the intervention, the large size of the monitor and sound of the alarm drew attention, potentially causing embarrassment and stigma. Due to perceived stigma, some PWTB adapted the intervention by leaving the monitor at home after

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removing the pills to ensure that someone else tracked usage, while the PWTB used alternative reminders such as cell phones to take their medication.

Conclusion

Although PWTB showed a positive attitude towards the intervention, perceived stigma contributed to participants adapting their lifestyle to meet treatment adherence requirements without using the monitor. However, the medication monitor was a tool that seemed to prompt this personal change in behaviour. Achieving people-centered TB care, including the introduction of DATs, will require that TB programmes incorporate PWTB insights to maximize their use and effectiveness.

Introduction

The treatment success rate for drug sensitive Tuberculosis (DS-TB) in South Africa remains concerning at 78% for new care recipients and people with TB (PWTB) that relapse [1], whereas the global target is set at 90% [2]. Reduced treatment success rates are due to sub-optimal treatment adherence, catalysed by stigma, forgetfulness, lack of support from friends and family, distance from clinics, lack of counselling and poor health worker-patient relationships [3].

The introduction of digital adherence technologies (DATs), such as medication monitors in TB programmes may support treatment adherence among PWTB. Medication monitors that remind PWTB to take their medication are less resource intensive and can monitor medication dosing patterns in real time [4]. Differentiated care approach (DCA) is a person-centered approach where services are adapted to the needs of PWTB, helping to shift utilization of resources to those who are in most need [5–7]. Medication monitors allow for efficient use of health system resources where allocation of resources can be re-directed to those who miss doses by offering tailored care packages in the form of differentiated care services [8].

Nevertheless, some medication monitors are bulky and have a loud alarm which may lead to unintentional disclosure of TB status thus interfering with adherence [9]. Despite this, one pilot study in KwaZulu-Natal (KZN) province SA, showed that use of medication monitors did not cause stigma or compromise confidentiality when pills were concealed [10]. The KZN study took place over three weeks period with hospitalised drug-resistant TB (DR-TB) individuals. Little is known if the findings from that study [10] would be similar amongst out-patients using medication monitors over a longer duration. Although, there is limited information on effectiveness of using a DCA, PWTB perceived healthcare workers (HCWs) as supportive when patient medication doses were monitored remotely [10].

Adoption of medication monitors relies on understanding end-user insights to refine implementation. However, there is limited evidence on the acceptability of medication monitors when combined with a DCA in PWTB. A formative study from Uganda where 35 PWTB were interviewed to elicit perceptions of using electronic monitors feelings about monitoring medication intake using a medication monitor (Wisepill device) and receiving SMS reminders supported acceptability. Real-time adherence interventions could potentially provide acceptable approaches to remind and motivate PWTB to take medication regularly. However, findings were limited since participants were asked about their perceptions before they could use the intervention in real life [11]. The care package in this study was limited to only SMS reminders.

As little is known about the lived experiences of end-users of DATs and DCA in PWTB, we evaluated the acceptability of using medication monitors (Wisepill evriMED 1000 device) prompting a DCA. The DCA involved short message service (SMS), phone calls, home visits and motivational counselling, among PWTB in South Africa. This evaluation was conducted as part of the TB Monitoring Adherence to Treatment Endpoints (TB MATE) study.

Methods

Study design and study setting

This exploratory qualitative study was nested within a cluster-randomized trial (CRT) implemented in 18 clinics across three provinces of South Africa: Gauteng (Ekurhuleni district); Western Cape (Klipfontein and Mitchell's Plain districts); and Kwa-Zulu Natal (eThekwini district) [8]. In the intervention arm of the CRT, participants received medication monitors with daily timed alarms and lights serving as reminders to take their medication incorporating a DCA in response to missed doses identified from a central database [8]. The alarm time was configured at enrolment as per the participants preference, but the alarm's volume and light intensity could not be adjusted. The DCA was implemented in a progressive manner depending on the number of doses a participant missed [8]. If one dose was missed, then a SMS reminder was sent to the participant [8]. If a second or third dose was missed, then study staff contacted participants telephonically; a home visit was conducted when the fourth dose was missed to provide motivational counselling [8]. An additional light on the medication monitor served as a reminder for monthly dispensing visits [8].

Site selection

The qualitative study took place in the nine intervention clinics, three in each province. Clinics were selected based on location, HIV prevalence and total number of PWTB starting TB treatment per month [8]. Adult HIV prevalence in the general population is 12.5% in Gauteng, 8.9% in Western Cape and 18.2% in Kwa-Zulu Natal province, according to the 2017 National HIV Prevalence, Incidence, Behaviour and Communication Survey [8,12].

Study population

The study population included men and women that were enrolled in the CRT, had drug sensitive TB disease and who are initiated on TB treatment, aged 18 years and older, and fell into adherence categories (green, orange or red). Those in the green category received an SMS, orange category received a phone call while those in the red category had received a home visit (Table 1). Participants were purposively selected by treatment month, gender and weekly adherence history for equal distribution across these attributes to ensure variation in the responses.

Conceptual framework and themes explored

We used the Technology Acceptance Model (TAM) [9] to develop an in-depth interview (IDI) guide that explored the following themes: (i) level of satisfaction with activities related to the

Table 1. Interventions.

Weekly Adherence	Weekly Doses missed	Adherence category	Intervention
85%	1	Green	Same day SMS reminder (automated)
45–84%	2 or 3	Orange	Phone call by nurse or counsellor
<45%	4 or more	Red	Home visit and/or clinic visit
Greater than one week with 4 or more missed doses			Recall for other adherence measures e.g. motivational counselling.

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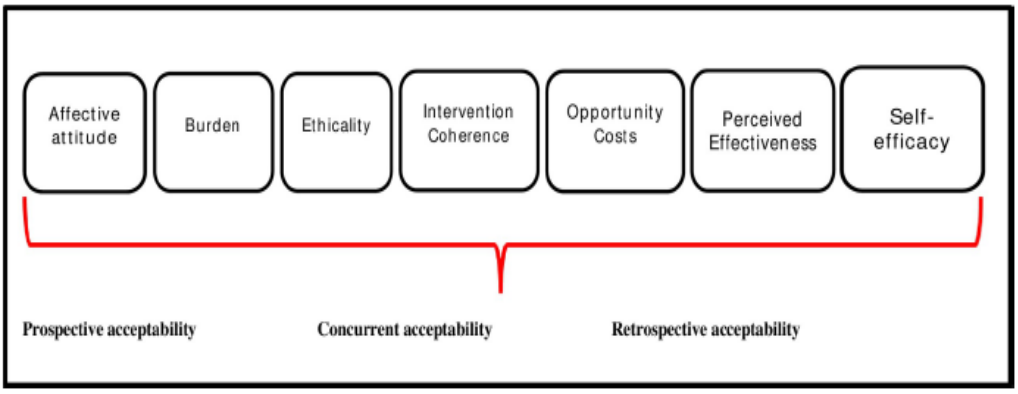

Fig 1. Theoretical Framework of acceptability (Sekhon et al 2017 [13]).

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differentiated model of care and use of the medication monitor technology; (ii) feelings and attitude toward use of the technology; (iii) reasons for accidental opening of the monitor (iv) ease of the use of the monitor; (v) perception and experience of receiving SMS's, home visits and motivational counselling; (vi) stigma; (vii) cultural or other barriers to uptake of the differentiated model of care. Using the Theoretical Framework for Acceptability (TFA) [13] shown in Fig 1 below, we explored prospective, concurrent, and retrospective acceptability (before, during, and after the intervention) across the sample attributes. We used two models as the emergence of inductive codes meant that the TAM was not adequate, and these codes would be best summarised using the TFA.

Data collection

From January to February 2020, we piloted the IDI guide with six participants, two males from the green category, two females from the orange category and one female and one male from the red category. Interviews were conducted face-to-face at a private area within the clinic and the data was included in the analysis. Minor adjustments were made to the initial guide to include additional background demographic questions. Data collection continued between July and October 2020. Each interview took 45–90 minutes. All interviews were conducted in the preferred local language of the participant by a male or female research assistant with qualitative training and experience who was accompanied by a note taker (either male or female). The researchers did not establish a prior relationship with the participant, though they carefully explained the information sheet enabling them to understand the reasons for the study. The interviews were digitally recorded following consent and transcribed verbatim by trained research assistants. The transcripts were not returned to the participant for comment or correction. Only the participant, interviewer and note taker were present during the interviews. Limited authorised staff and study investigators had access to information that could identify individual participants during or after data collection. Saturation was assessed during data collection through debrief sessions with data collectors, by asking the same question in different ways and reviewing a sample of the recordings until no new information emerged. No repeat interviews were carried out.

Data analysis

We used thematic analysis including deductive and inductive approaches [14,15]. At least 10% of the transcripts were coded by two independent researchers (BA and RM) to reduce bias and

improve reliability [14]. A codebook of emerging themes was developed, guided by the framework on the 'Theoretical Framework for Acceptability' [13]. Where there was no inter-rater agreement, the theme was dropped [14]. The final codebook was used to code the remaining transcripts and any new codes that emerged were included. MAXQDA qualitative software was used for the coding process. We present the major themes that emerged and use supportive direct quotations from participants. Participants did not provide feedback on the findings.

Ethics approval and participant consent

The parent study received ethics approval from the three district and provincial ethics committees where the trial sites were located. This qualitative study was approved by the Human Research Ethics Committee (HREC) of the University of Witwatersrand (Ref 180705) and the University of Cape Town (Ref 452/2018). We obtained written informed consent for study participation and permission for digital recording from all participants. Participants were reimbursed for their time and transport related to the interview.

Results

We selected 85 PWTB, and 62 were interviewed. Twenty-three 23 PWTB either declined to participate (n = 6), could not be reached (n = 12) or were not fit to participate (n = 5). Out of the 62 interviews conducted, we analysed 61 in total across 3 provinces. One interview was excluded from the analysis since the participant was below 18 years and did not meet the inclusion criteria. Across the three provinces, majority (55.74%) of the PWTB were male (n = 34). Table 2 below shows the distribution of the treatment month and the adherence categories.

Major themes that emerged on the use of the monitor and the DCA that aligned to the TFS framework constructs [12] included: (1) positive attitude towards using the medication monitor and receiving the DCA support; (2) burden and adaptability to the medication monitor; (3) intervention coherence and self-efficacy; and (4) perceived effectiveness of the intervention.

Major Theme 1: Positive attitude towards using the medication monitor and receiving the DCA support

PWTB across adherence categories showed a positive attitude towards using the monitor and receiving the DCA support. The quotations below show that phone calls and SMSs were well accepted as PWTB felt that providers cared for their health.

> *"There is nothing I don't like about the box. I like this box a lot because it helped me a lot, if it wasn't for it, I don't think I would be here today."*–***Female, 23 years, Gauteng, Orange category***

Table 2. Characteristics of study participants.

	Gauteng (n = 20)	KwaZulu-Natal (n = 21)	Western Cape (n = 20)
Female	9 (45%)	6 (29%)	12 (60%)
Treatment month <2months	2 (10%)	4 (19%)	5 (25%)
Treatment month <2–6 months	18 (90%)	17 (81%)	15 (75%)
Adherence category			
• Missed 1 dose a week (Green)	5 (25%)	13 (62%)	7 (35%)
• Missed 2 or 3 doses a week (Orange)	8 (40%)	6 (29%)	7 (35%)
• Missed 4 or more doses a week (Red)	7 (35%)	2 (10%)	6 (30%)

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"I liked being called and being sent SMSs and it might happen that you have forgotten to take your pills and you'd be reminded by being called and asked why you didn't open the box. . . Then you will go take your pills and remember that you had not opened the box."—***Female, 37 years, KwaZulu-Natal, Orange category***

"It felt good knowing that there were people who cared for me and were looking out for my health besides my family."—***Male, 36 years, Western Cape, Red category***

However, few PWTB were upset due to the timing of the text message and home visits especially among those who perceived stigma by their neighbours.

"I don't want to lie. I didn't like those SMSs. They irritated me because I had taken them at 9. You've opened it [referring to the medication monitor] and took pills, then closed it."–***Female, 25 years, Western Cape, Green category***

"It [referring to home visits] made me to be feel shy. It made me think as if they are gossiping about me or all things of sort that was what I was thinking."–***Male, 18 years, KwaZulu-Natal, Orange category***

Major Theme 2: Burden and adaptability to the medication monitor

Some PWTB did not like the monitor alarm and made alternate arrangements to take their medication as described in the quotations below.

"In the first week I was using this box. . . when I am on the way or I am in a taxi and it rings at 09:00, I would be embarrassed. I would open and close it. The person sitting next to me would be alarmed by what is ringing in this persons' bag."–***Male, 37 years, Western Cape, Red category***

"It is just that it once happened that. . . it went off in their [referring to friends] presence, they did not have a problem with the noise, it was not that annoying, it's just that I did not want them to know that I take treatment for TB."–***Male, 30 years, KwaZulu-Natal, Green category***

"I will not take it wherever I go. When I am visiting a relative to sleep there and come back tomorrow, I leave the box at home. I will not go around with the box. The one who is at home I tell him that when the box ring at 09:00 open it and close. They do what I tell them to, it is like I am with them. When I open it and close it, it has recorded that I have taken my medication."–***Male, 67 years, KwaZulu-Natal, Green category***

There were mixed views on features of the medication monitor described by the quotations below.

"So the only thing I don't like about it is that it's not very mobile neh so it's like if I have like somewhere to go to. . .and I don't need anything else besides my phone, my phone is this size, the bag I'm carrying is literally that size as well. . . I don't have enough space so the only problem I have with it is, I can't carry on with it everywhere I go, it's big."—***Female, 21 years, KwaZulu-Natal, Orange category***

However, some PWTB had no concerns with the loud alarm and large size of the monitor

"No, I am not bothered as to what people have to say because it is for my health and they will always talk and that is all they can do, talk."–***Male, 25 years, Western Cape, Orange category***

"This is my life, I can't hide this box or hide my medication because I'm around people at work, visiting relatives or anywhere."–***Male, 31 years, Gauteng, Red category***

Major Theme 3: Intervention coherence and self-efficacy

Most participants understood the intervention, how it worked, and were able to describe the meaning of the lights fitted on the monitor. The participants described the monitor as a —"smart box", "alert box", "lunch box", "amazing", "container" (because of its large size), "piano" or "big phone" (because it rings).

"I also call it lunch box. I say "give me my lunch box, I want to take my medication."

–Female, 33 years, Gauteng, Red category

"This box really helps because when it is time to take your medication, it reminds you and you also decide that you are too scared that it might alert the clinic that you did not open the box or whatever. It was one of the things that I was personally afraid [mindful] of."–***Male, 37 years, Western Cape, Red category***

"You just tell yourself: "you know what? Let me just drink my medication and. . . I will. . . live a healthier life. So that's what I want".–***Male, 37 years, Gauteng, Green category***

Even though some participants felt like they were being watched, the monitor helped these participants adhere to treatment.

"This box helps me. I don't go out without taking my medication. This box must ring first before I go out. It must ring first before I go out."–***Male, 49 years, Gauteng, Orange category***

"I never felt [found] ashamed or my TB situation whatsoever because I also get support I also know that. . .as long as I follow instructions from the clinic about medication so they always support me by calling me that's the support I get from the clinic."

–Male, 43 years, Gauteng, Orange category

The participants understood that if they did not take their medication, then an SMS, phone call and home visit would follow.

"What I see, if I forget to take the pills, at the clinic they call, they send me an SMS reminding me. If they see that I haven't taken them the next day they call."–***Female, 37 years, Kwa-Zulu-Natal, Green category***

"No, I was told that if I do not take my medication once or twice that they will send me a message. If I do not take it after that then they will give me a call or come to my house."–***Male, 25 years, Western Cape, Orange category***

The PWTB felt confident that they could perform the behaviors required to participate in the intervention and they showed willingness to participate due to the perceived benefits.

"I was then asked if I would not have any issues if I used this box. I said, no I would not have a problem because it would help me in the long run."–***Male, 37 years, Western Cape, Red category***

Major Theme 4: Perceived effectiveness of the intervention

PWTB accepted the intervention due to their desire to get healed and not spread TB to close contacts, as supported by the quotations below.

> *"Eeh because I wanted to get healed and I didn't want TB to have more powers and even people I stayed with get infected."*–***Female, 48 years, Gauteng, Orange category***

> *"At first, I was quite surprised. I wondered why they would give me a box instead of just the treatment, but after being told about its purpose, I realized it would be helpful and my family was supportive about it at home."*–***Male, 36 years, Western Cape, Red category***

> *". . .I can feel that I am better than before, I was sick but now I can feel that I am getting better I can walk which means the box is working."*–***Male, 36 years, KwaZulu-Natal, Green category***

It was apparent that PWTB placed high value on the monitor, with some using it as a safe storage not only for their TB medication but also for other personal valuable items.

> *"I am imp- impressed for having the box in such a way that, I even place my I.D [referring to identification document] inside and my other valuable items everything."*–***Female, 19 years, KwaZulu-Natal, Green category***

Even those who were in the red adherence category and had missed a few doses still appreciated the technology and the additional reminders from the SMS notifications.

> *"I don't know how it notify them but I feel that they are able to find out in some way. If my box didn't ring they are able to see that I'm not taking my medication correctly, this box is a proof that am I doing the right thing by taking my medication."*–***Male, 31 years, Gauteng, Red category***

> *"But the SMS. . .because as I might add that I am always with my phone. When it says "ti-ti" it just means something, I say "oh" so fast and immediately I remember."*
>
> *–Male, 30 years, KwaZulu-Natal, Green category*

Home visits were viewed by some PWTB as being beneficial not only to themselves but also to the entire family. The desire to share the benefits of the intervention was also seen through PWTB who recommended friends and family with symptoms of TB to ask for the monitor at the clinic, if they received a TB diagnosis.

> *"I don't mind them [HCWs] coming home because it's not just me who benefit, my family benefits as well."*–***Female, 37 years, KwaZulu-Natal, Green category***

> *"All I can tell him/her is that they must go to the clinic and find out if he/she has TB and ask for the box. This box will help him/her remember his/her dates and will also help her keep his/her pills safe, undamaged and not lost."*–***Female, 37 years, KwaZulu-Natal, Green category***

Discussion

Our study found that the use of medication monitors (Wisepill evriMED 1000 device) with a differentiated care approach (DCA), was acceptable among PWTB. Through the four major

themes which emerged from our study, we found that PWTB had a positive attitude to both the monitor and the DCA. They appreciated the reminders, social support and assistance with accepting their TB diagnosis. This finding is similar to the study from Kwa Zulu-Natal where participants reported positive experiences from using the electronic pillbox [10]. Likewise, the formative study done in Uganda found that the medication monitor, an earlier version of Wisepill device, was acceptable and participants felt that being monitored enabled them to demonstrate their commitment to adherence [11].

However, we found that some people felt burdened by the idea of moving around with the monitor due to the alarm sound and size which could lead to disclosure of their TB status. A similar finding was seen in India amongst Multidrug-resistant TB (MDR-TB) patients using a similar medication monitor (the Medication Event Reminder Monitor—MERM) where lower acceptance of the medication monitor was related to its large size causing difficulties in portability and storage [16]. The PWTB in India also removed the medication from their device to avoid any stigma and discrimination when moving around [16]; and recommendations suggested that future improvements to the design of the medication monitor could improve the consistent use of the medication monitor [16]. Optimizing the design of the medication monitor is a recommendation that has also been cited as a means to improving acceptability in earlier versions of the MERM that were used to improve adherence to antiretroviral therapy (ART) [17]. Various design options related to the monitor's size and alarm should be considered based on the preferences of different groups of PWTB such as those who are homebound, travellers, stigmatized etc.

We found that PWTB in our study had good intervention coherence and self-efficacy as they understood how the monitor worked and what to expect if they did not open it upon the alarm ringing. Most of the participants found the monitor easy to use and felt that they should "obey the rules' not only out of fear that the provider was watching them but also because they were keen to live a healthier life. They felt confident to perform the required actions and found the monitor and DCA effective in helping them adhere to treatment. This finding is different from the study done in India where PWTB had incorrect understanding of the MERM due to sub-optimal counselling which may have led to incorrect use of the medication monitor [16]. However, a recent meta-analysis of a survey conducted in six countries showed that PWTB had a favourable impression of their capability to use DAT (including Wisepill evriMED in Ukraine and South Africa) which was facilitated by knowledge that the DAT was a tool to help PWTB remember to take their medication and improve their adherence [18].

Our study fills an important gap in the literature that assessed the acceptability of the DCA among outpatients. Since the studies from KwaZulu-Natal [10], Uganda [11] and India [16] did not assess DCA, this is a novel finding to our study. Another strength is that our study had a large sample size of 61 interviews and was carried out in three geographically and culturally diverse provinces of South Africa which makes the generalizability high for South Africa. Additionally, the PWTB were interviewed in various months of treatment and were receiving treatment as outpatients which gives us insight into their lived experiences.

Our study did have some limitations. The study evaluated the implementation of the medication monitor within a trial, which, although conducted at routine primary care clinics, was supported by research staff which may have led to an improved experience by the participants. Practical parts of the intervention were that we did not offer the participants any incentives for using the monitors and most home visits were conducted by outreach teams that routinely work in the communities. In the routine setting, home visits are usually conducted by Ward Based Outreach Teams (WBOTs) where the clinic-based TB nurse gives the WBOTs a list of PWTB who have missed their clinic appointments and need to be traced [19]. Given that there is no way of finding out whether the PWTB is still taking their treatment, consideration should

be given to integrate aspects of our intervention such as the medication monitor, SMSs and phone calls into the National TB program (NTP) as initial steps to reminding PWTB to take their treatment before WBOTs embark on home visits.

Conclusion

This study gives us an understanding of the experiences of persons with TB using medication monitors and DCA. Achieving people-centred TB care, including the introduction of DATs and DCA, will require that TB programmes incorporate patient insights to maximize their adoption and effectiveness. Features of the monitor such as size and the alarm which PWTB felt drew attention to their TB status, potentially causing embarrassment and stigma, would need to be addressed before scale-up as they may serve as a barrier to acceptability. It seems the home visits were also not particularly well received and further examination is needed to determine whether these were beneficial. A key highlight from our study is that despite some challenges most PWTB found the medication monitors and DCA as acceptable approaches to supporting medication adherence.

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CHAPTER 6: THE COST-EFFECTIVENESS OF THE INTERVENTION FROM A SOCIETAL PERSPECTIVE

6.1 Introduction

This was a quantitative paper that showed the costs of implementing the Wisepill evriMED device and the differentiated model of care from three perspectives: PWTB, health system and societal. The paper discusses various ways in which the costs can be reduced and also highlights that medication monitors and DCA can be considered a cost-effective option for scale-up given that the intervention had a significant impact on adherence. Further details are provided within the paper.

6.2 Paper 3: Cost-Effectiveness Analysis of implementing Wisepill evriMED device and differentiated care approach in South Africa

Cost-Effectiveness Analysis of implementing a medication monitor and differentiated care approach among people with TB in South Africa

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Abstract

Background

Digital Adherence Technologies (DATs), with a Differentiated Care Approach (DCA), may improve adherence to tuberculosis (TB) treatment. Within the TB Monitoring and Adherence Endpoints pragmatic cluster-randomised trial, we evaluated the cost-effectiveness of using a medication monitor (Wisepill evriMED 1000 device) to inform a DCA involving text messages, phone calls and home visits in three provinces of South Africa.

Methods

We conducted a cost-effectiveness analysis from a societal perspective at six clinics, one intervention and one standard of care (SoC) clinic per province (June 2019-August 2020). Health system costs were collected using a bottom-up activity-based costing approach involving time and motion studies. People with TB (PWTB) were interviewed on costs related to accessing the intervention. Adherence was measured using patients ≥80% adherence overall. Unit costs were calculated as cost per patient treated for TB while incremental cost-effectiveness ratio (ICER) was calculated as cost per additional adherent PWTB.

Results

With 1278 PWTB in the intervention arm and 1306 PWTB in the SoC arm, effectiveness was 81% and 50.8% in the intervention and SoC arms respectively. The total cost per patient treated for TB was $103.93 - $199.87 (intervention) and $44.89 - $131.22 (SoC), resulting in a societal incremental cost of $49.73. Patient costs were $38.98 - $117.94 per patient (intervention) and $35.92 - $91.94 per patient (SoC) with indirect costs (foregone income) contributing to a large proportion of total costs at three intervention (56.7% - 69.8%) and two SoC (69% and 77.4%) clinics. The ICER was $166.33.

Conclusion

The cost of achieving an additional adherent PWTB was estimated at $166.33. and DCA can be considered a cost-effective option for scale-up if we negotiate a lower cost for monitors with manufacturers and ensure re-use of the devices, helping reduce health systems costs.

Introduction

Globally, evidence on Digital Adherence Technologies (DATs) on improving adherence to Tuberculosis (TB) treatment on a large scale is increasing, as reducing missed doses is becoming an important determinant of treatment completion and post-treatment relapse [1]. . A recent systematic review looking at the impact of DATs on health outcomes showed that overall, the use of DATs was associated with more frequent treatment success in TB disease (OR = 1.18 [1.06, 1.33] and a decrease in loss to follow up (OR = 0.71 [0.53, 0.94][2]. A modelling study done in India showed that new DATs reduced missed doses and decreased TB incidence by 12% [1]. These authors acknowledged that cost and cost-effectiveness analysis of DATs would be important [1].

As evidence on effectiveness of DATs is increasing, there is still limited evidence on their costs and cost-effectiveness which makes it difficult to include them in policy and planning decisions in national TB control programmes [3, 4]. Cost analysis may guide which DAT to prioritize or which populations to prioritize to allow for scarce resources to be utilised efficiently. Large costing studies on DATs have been conducted in China and Ethiopia: large randomized controlled trials measured effectiveness and cost-effectiveness of using a medication monitor to improve clinical outcomes amongst people with drug-sensitive TB (DS-TB) [5-7]. The study done in China found that reminders reduced non-adherence by 57-64% in the intervention group compared with the control group [5]. In a setting in China where DATs were not being used to support treatment monitoring, total treatment costs tend to be high due to long travel time for home visits by health staff for treatment supervision often leading to non-adherence in the long-term [8]. Thus both treatment support and financial support are key to improving adherence to treatment for people with DS-TB who have high total treatment costs (defined as direct costs of self-paid TB drugs, liver protecting

and cough remission drugs, travelling and accommodation)[8, 9]. However, the health system in China is organised differently from South Africa and other African countries which may have an influence on the costs of implementation and thus the results are not easily generalizable across different settings.

Other DATs that have been evaluated include 99DOTS which uses a medication blister pack that reveals a unique toll-free phone number when people with TB (PWTB) remove pills [10]. PWTB call the number, and an automated system records their dose confirmation in real-time [10]. A cost-effectiveness study done in Uganda on 99DOTS found the incremental cost-effectiveness was $355 per incremental treatment success and the intervention was found to be effective in the per-protocol population where 52% of PWTB enrolled on 99DOTs contributed to analysis giving an adjusted OR for successful treatment outcome of 2.9 (95% CI 1.6-5.3) versus the control phase [11]. The study found that if sustained over a 5-year period and scaled up, 99DOTS can be a cost-effective option for TB treatment adherence support in high TB burden settings like Uganda [11].

The gaps in DAT research in South Africa include limited evidence on costs and other important factors that may influence successful implementation. To the best of our knowledge, few costing studies on DATs use have been conducted in South Africa [12-14]. One study done in the Northern Cape Province of South Africa on digital pillboxes showed cost savings from reduced TB treatment failure [12]. However, this study was not sufficient to inform broader consideration across South Africa since it was designed as a cost-minimization analysis using data from a small-scale pilot. Another important gap that other authors have highlighted is the need to understand the economic burden that "free" TB care

places on PWTB through non-medical direct costs such as transportation to clinic visits and which DATs has the potential to address through reduced clinic visits [13].

Given the gap in evidence, we undertook this costing study within the larger parent study known as TB Monitoring and Adherence Endpoints (TB MATE) [14], a cluster-randomized trial evaluating medication monitors for improving TB adherence in people with drug-sensitive TB. The objective of this costing study was to understand the costs and cost-effectiveness from the societal perspective of implementing the medication monitors and differentiated care approach in South Africa. This study will contribute to policy decisions on large-scale implementation of DATs in South Africa and other resource-limited settings.

Methods

Setting and results for the primary outcome of the trial

The TB MATE cluster-randomised trial evaluated whether the implementation of a medication monitor (Wisepill evriMED 1000 device, available at https://www.wisepill.com), coupled with weekly monitoring and differentiated care, could improve adherence, reduce poor treatment outcomes and recurrence in people undergoing DS-TB treatment [14]. The trial was implemented in 18 primary health clinics; six clinics in each of the three provinces of South Africa, Gauteng (Ekurhuleni district), Western Cape (Klipfontein and Mitchell's Plain districts) and Kwa-Zulu Natal (eThekwini district) [14]. Clinics were randomised 1:1 to the DAT intervention or SoC. Adults and children ≥2 years old with clinically or microbiologically diagnosed drug-sensitive TB and had initiated TB treatment within the last 14 days were eligible for enrolment. At intervention clinics, participants were provided with a medication monitor and a differentiated care approach (DCA) was implemented. In the SoC clinics, participants received a silent monitor to measure adherence with data not available to the care providers and received treatment using the routine approach. The intervention was implemented by TB nurses at each clinic and research study staff ("study staff" thereafter) from the implementing partners (Aurum Institute, Johannesburg; University of Cape Town, Cape Town; Interactive Research and Development, Durban).

The primary outcome of the trial was a binary outcome of having ≥80% adherence, measured using daily data from the monitor, with a monitor opening as a proxy for treatment adherence. The geometric means across clusters for the percentage of PWTB satisfying the primary outcome was 81.0% (1056/1306) and 50.8% (650/1278) in the intervention and SoC arms respectively, giving an adjusted risk ratio of 1.5 (95% confidence interval 1.4-1.7,

Data collection and analysis of patient costs

As part of the main trial, participants enrolled at each of the 18 clinics (a total of 2610 participants) were interviewed at baseline where their demographic information was collected. A sub-sample of these participants from 6 clinics were then interviewed by a trained research assistant at the end of each treatment phase. At each clinic, we used random sampling to select 55 participants in each treatment phase. The interviews were conducted at the month 2 visit (end of intensive phase) so as to capture the pre-treatment costs and around the 6-month follow-up visit (end of continuation phase) by use of a questionnaire. A sub-sample, randomly selected, was used due to resource constraints. The questionnaire was adapted from the REACH (Researching Equity in Access to Healthcare) project that was a multi-centre study that estimated the true costs of health care utilization for PWTB receiving 'free' HIV/TB care and treatment in rural KwaZulu-Natal [22] and the World Health Organisation TB Patient Cost Survey [23]. Patient costs were calculated in both trial arms across various categories such as utilization of services and affordability of health care [22]. The questionnaire was piloted on a few participants before the official data collection began.

Economic costs were measured where both direct and indirect costs related to the PWTB accessing the intervention were assessed. Direct medical costs included drugs, lab tests etc. while direct non-medical costs included childcare, overnight accommodation, food during visit etc. Indirect costs were assessed through questions on travel time, waiting time, personal and household income, losses incurred by the PWTB as a result of illness such as days off work, lost wages and financial coping strategies such as loans. All data was entered into a database created in REDCap. Data were exported from REDCap into STATA (version 14, StataCorp LP, College Station, Texas) for analysis. Direct and indirect costs were summarised by way of means and standard deviations for normally distributed data.

Description of the interventions

In the intervention arm, enrolled PWTB received standard patient education and a medication monitor (Wisepill 1000 evriMED device) programmed to alert them, using audio and visual reminders, to take their medication daily and return to the clinic monthly for medication refills [14]. The DCA involved automated SMS reminders which were sent to PWTB with a missed dose, based on the proxy of the medication monitor not being opened [14]. A second or third missed dose in a week triggered a study staff-initiated phone call to the PWTB, and four or more missed doses in a week triggered a home visit by study staff [14]. When PWTB visited the clinic for their usual dispensing visit, the study staff showed them their own adherence data and discussed their medication adherence history which was available in real time [14]. The study staff who implemented the intervention were trained Research Assistants (RAs) with a high school qualification or a bachelor's degree working for the implementing partners.

PWTB in the SoC arm received the standard patient education and medication monitor but it was not configured to have visual or audio reminders for pill intake or refills [14]. Medication monitor use data collected on the system were not reviewed by study staff during follow-up study visits though PWTB received counselling regarding their TB treatment as per SoC [14].

Fig 1: TB MATE Intervention. Differentiated Care Approach.

Comparators

The costing study compared the costs of implementing the medication monitor and DCA in the intervention arm versus implementing routine care (SoC arm). Routine care did include participants using a monitor in silent mode to enable adherence to be measured; the cost of the medication monitor was removed from this group.

Data collection and analysis of patient costs

A sub-sample of the main trial participants from the six clinics was interviewed by a trained research assistant at the end of each treatment phase. At each clinic, we selected 55 participants in each treatment phase by means of random sampling where we approached every second participant and invited them to participate in the survey. The interviews were conducted at the month 2 visit (end of intensive phase) so as to capture the pre-treatment costs and around the 6-month follow-up visit (end of continuation phase) by use of a questionnaire. A sub-sample per clinic was used due to resource constraints. The questionnaire was adapted from the REACH (Researching Equity in Access to Healthcare) project, a multi-centre study that estimated the true costs of health care utilization for PWTB receiving 'free' HIV/TB care and treatment in rural KwaZulu-Natal [16] and the World Health Organisation TB Patient Cost Survey [17]. Patient costs were calculated in both trial arms across various categories such as utilization of services and affordability of health care [16]. The questionnaire was piloted on a few participants before the official data collection began.

Economic costs were measured using both direct and indirect costs related to the PWTB accessing the intervention. Direct medical costs included medicines and clinic fees while direct non-medical costs included childcare, overnight accommodation and food during visit. Indirect costs were assessed through questions on travel time, waiting time, personal and household income, losses incurred by the PWTB as a result of illness such as days off work, lost wages and financial coping strategies such as loans. Data were entered into a REDCap database and imported into STATA (version 14, StataCorp LP, College Station, Texas) for analysis. Direct and indirect costs were summarised by way of means and standard deviations for normally distributed data.

Data collection of health system costs

Health system costs were collected between June 2019 - August 2020 using a bottom-up activity-based costing approach. As part of this approach, a time and motion study was conducted at the clinic level where providers were directly observed consulting with PWTB at their various monthly clinic visits. We performed a minimum of 10 cross-sectional observations of the TB nurse and the study staff for the enrolment visit and at each of the monthly visits (that occurred over the six-month treatment period) with a total of 70 observations per clinic. We conducted another 10 observations for home visits in each of the three intervention sites. Study staff were also interviewed on activities that were not possible to observe by the researchers such as generating automated reports from the Wisepill website, calling the PWTB or tracing the participants to complete a home visit and conducting home visits. For the intervention arm, as this was how the intervention was implemented in the project, we assume a single use per monitor.

We excluded any time spent on research activities from the costs calculated. The costs of drugs and laboratory tests were not calculated as these were not part of the intervention and were the same in both arms. In addition, at SoC sites, the cost of the medication monitor, the platform hosting the data on monitor use by the PWTB and DATs training were excluded as these were only given for adherence measurement as part of research activities and would not normally be implemented as SoC. Financial data needed for costing the intervention including salaries of the implementing study staff obtained from financial records kept at the implementing partners' offices. Department of Health nurse's salaries for clinic staff were estimated from a public portal. Data on the prices of supplies and equipment were obtained from invoices for those items purchased by the project. We only included visit data for those visits that took place in person with the study staff. If the study staff member missed the

participant when they came to the clinic and then later called them for a telephonic visit, then that visit was not included.

Data analysis of health system costs

Health system costs were analysed and reported according to internationally accepted standards where the cost per person with TB and incremental costs of using the evriMED device and differentiated care approach as compared with the current SoC in South Africa were measured within each province [18]. Shared costs such as data management support from the implementing partners were allocated to PWTB using the proportion of PWTB enrolled at the intervention site to the overall enrolment at all intervention sites. Capital costs of inputs lasting longer than 12 months such as training and equipment were annualised over 3 years using a discount rate of 3% [19]. We assumed that the monitor was used once in the baseline scenario. A sensitivity analysis was conducted by altering the values of key variables where we assumed the following; (i) the monitor was re-used three times; (ii) adherence monitoring was done by a TB nurse instead of a research assistant, as this was the cadre of staff more likely to implement in routine practice; (iii) the Wisepill platform hosting for 153,000 PWTB i.e. the total population treated for DS-TB in South Africa (180,000) [20] and allowing for 85% uptake.

Societal costs and Cost-Effectiveness Analysis

For each arm, the mean cost to the patient was added to the mean cost to the health system to obtain the average societal cost. The primary outcome was reported as cost per additional adherent PWTB.

To calculate the Incremental Cost-Effectiveness Ratio (ICER), the average societal cost was multiplied by the study population resulting in the total costs for each arm. The difference in

total costs by study arm was divided by the difference in the percentage with the primary outcome (binary outcome of having ≥80% adherence) by study arm. The ICER for every additional patient with ≥80% adherence was compared to other interventions. This was used to guide the decision on implementation beyond the trial period since no locally relevant threshold exists for SA. All costs were converted from SA Rand (ZAR) to the 2020 United States Dollar (USD) for ease of international comparison using 1 USD = 16.46 SA Rand [15].

Results

Table 1 highlights the demographic characteristics of the 369 participants who took part in the patient costing survey in the six clinics. Most of the participants were male (56.1% – 71.8% across clinics), mean age overall was 36.8 years (33 - 40 years by clinic), the majority of the participants were black African at 97.6% (93.6% - 100%), unemployed at 54.84% (52.6% - 77.5%), and never married/single at 64.9% (51.6% - 94.7%). The head of household (HHH) was more likely to be female in KwaZulu-Natal (55.3% and 65.8%) and Western Cape (52.4% and 60.3%) versus Gauteng (35.2% and 29.5%) provinces.

Table 2 shows the patient costs that PWTB experienced during treatment. Mean total patient costs ranged from $38.98 - $117.94 per patient in three intervention clinics and $35.92 - $91.94 per patient in three SoC clinics. In five sites the largest contributor to patient costs were indirect costs (foregone income) where 56.7% - 77.4% of total costs were indirect. In the sixth site where direct non-medical costs were the largest contributor to patient costs, this was mostly driven by the cost of special food (58.1%) purchased during treatment.

The mean number of visits per participant over the six-month treatment period were between 1.6 - 3.5 visits across the clinics (table 3). This resulted in clinic costs ranging between

292 $8.97-$39.28 per patient in the SoC arm and $64.95-$81.93 per patient in the intervention
293 arm (table 5).
294
295 The largest drivers of the incremental cost to the health system (table 5) were the medication
296 monitors and accessories (battery, modules and dispenser SIM card) at $24.38 (57%), data
297 management support at $7.41 (17%), Wisepill platform hosting at $3.7 (9%) and home visits
298 $5.99 (14%). The total cost per patient (from a health system perspective) ranged between
299 $64.95 - $81.93 (intervention) and $8.97 - $39.28 (SoC). The base case incremental cost of
300 the intervention (cost in intervention clinic minus cost in SoC clinic), ranged between $37.99-
301 $57.42 across the three provinces. All the key assumptions and parameters used are shown in
302 table 4.
303
304 Table 6 shows three sensitivity analyses allowing for device reuse of three times, the use of a
305 TB nurse or the sharing of platform hosting for 153,000 PWTB. Across all three provinces,
306 the decrease in total costs (compared to the base case) is seen when the device is re-used
307 three times at intervention clinics with incremental costs to the health system reducing to
308 $21.73 - $41.17 across the three clinics (table 6). The other two scenarios gave similar results
309 to the base case.
310
311 In table 7 the total societal cost in the intervention arm ($185 243.04 was greater than in the
312 SoC arm ($117 712) resulting in a total incremental difference of $67 530.72. The
313 effectiveness of the intervention (patients ≥80% adherence) showed an incremental difference
314 of 406 per patient. This resulted in an ICER of $166.33 per patient with ≥80% adherence.

315 ## Discussion

316 Our study found that incremental costs to the health system of implementing the medication
317 monitor (Wisepill 1000 evriMED device) and differentiated care approach in South Africa
318 was between $37.99 - $57.42 per patient across the three provinces. The sensitivity analysis
319 showed that this incremental cost can be reduced to $21.73 - $41.17 if the device is re-used
320 three times. The use of an alternative cadre (TB nurse) would result in an increased
321 incremental cost of $40.30 - $58.89 while platform hosting for all PWTB would range
322 between $35.93 - $55.36. The incremental cost of the intervention was mainly influenced by
323 four key drivers which were the cost of the monitors, data management support for the
324 platform, Wisepill platform hosting and home visits.
325
326 When we compared the proportion of costs that the monitor adds to the cost of treatment we
327 found the following; the cost of DS-TB drugs in an upper middle-income country like South
328 Africa is about $107 [21] and adding the societal incremental cost of the medication monitor
329 and DCA $166.33 increases this cost by a relatively small amount. The patient costs showed
330 that indirect costs (foregone income) contributed to a large proportion of the total patient
331 costs as PWTB often had to miss work to attend clinic visits resulting in productivity losses.
332 Other contributors to total patient costs were the amount of money that PWTB spent on
333 special food during treatment and transport costs to the clinic.
334
335 From results of this trial, we found a 30% increase (adjusted risk ratio of 1.5) in the
336 proportion of those who adhere to treatment defined as ≥80% adherence, as measured by
337 monitor openings [22]. Even though the TB MATE trial did not show any effect on treatment
338 outcomes [22], other studies have shown that adherence may affect clinical outcomes since

lower non-adherence were associated with significantly increased risk for unfavourable outcomes [23, 24].

Our study had several strengths. Firstly, our costing study filled an important gap in the literature since we evaluated the cost of a medication monitor and DCA for supporting patient adherence; this is particularly relevant within a high TB and HIV setting like South Africa where co-morbidities are likely to influence adherence patterns and health system costs. Secondly, we used a detailed bottom-up costing approach; this will allow subsequent comparisons with other settings since we provide a breakdown of all the costing ingredients. Lastly, the study was conducted in three provinces in South Africa, which enabled us to understand the effect of variability in operational management on health system costs.

Our study did have limitations which may reduce the generalizability of our findings. Adherence was measured using a proxy of monitor openings. The TB MATE trial did not show an effect on treatment outcomes and recurrence which is a better measure of treatment success. In the SoC arm some follow-up activities may have taken place in the routine setting such as home visits and telephone calls for non-adherent PWTB, which we were unable to observe and include within our costing study; this would have resulted in an underestimation of the costs in the SoC arm. Had these costs been included, they would have reduced the difference between intervention and SoC arms and so the ICER could have been lower.

Our study estimated societal costs for incorporating DATs and DCA into TB patient management as part of a large pragmatic RCT, however our sensitivity analysis suggested; that more research is required to explore implementation approaches as these will ultimately

lower the cost of DAT and DCA to the health system. At a minimum, we need to negotiate lower cost for monitors from available manufacturers and to ensure the re-use of the device at least three times. Other considerations that should be made before the scale-up of DATs and DCA is to increase efficiencies in data management and escalation activities such as home visits. Also, there is a need to reduce the number of clinic visits for those who adhere so as to lower the productivity losses incurred by PWTB.

Conclusion

The cost of achieving an additional adherent PWTB was estimated at $166.33 The additional outcomes were achieved at a reasonable additional cost hence medication monitors and DCA can be considered a cost-effective option for investment and scale-up [25] if we negotiate a lower cost for monitors with manufacturers and ensure re-use of the devices, helping reduce health system costs. As TB programmes re-invigorate their commitments to achieving TB elimination recovering lost ground from the Covid-19 pandemic, every aspect of the TB care continuum will need to be optimized; the importance of PWTB successfully completing TB treatment should not be understated. DATs may have a role to improve clinical outcomes for patients [14], however, like any innovation, societal costs will underpin the decision-making process and thus ways to reduce these should be prioritized to maximize scale-up.

383 Table 1: Demographic characteristics of participants and head of household, by region, participating in the patient costing survey

384

	Gauteng		KwaZulu-Natal		Western Cape	
N=369	Site 1 (n=91)	Site 2 (n=78)	Site 3 (n=40)	Site 4 (n=38)	Site 5 (n=61)	Site 6 (n=61)
	Intervention	SoC	Intervention	SoC	Intervention	SoC
Female, n (%)	31 (34.1%)	22 (28.2%)	18 (43.9%)	15 (39.5%)	21 (33.3%)	27 (42.9%)
Female HHH, n (%)	32 (35.2%)	23 (29.5%)	27 (65.9%)	21 (55.3%)	38 (60.3%)	33 (52.4%)
Mean age (std dev)	38.82 (15.6%)	40.22 (12.4%)	33.18 (16.0%)	33.07 (17.6%)	36.82 (12.2%)	34.46 (8.9%)
Mean age HHH (std dev)	48.98 (14.4%)	44.60 (10.5%)	48.95 (11.7%)	47.89 (11.4%)	51.18 (16.6%)	56.19 (12.4%)
South African, n (%)	85 (93.4%)	68 (87.2%)	40 (100%)	38 (100%)	61 (100%)	56 (91.8%)
Black African, n (%)	90 (98.9%)	78 (100%)	39 (95.1%)	37 (97.4%)	62 (98.4%)	59 (93.7%)
Education (highest grade passed 1-12), n (%)	63 (80.8%)	71 (78.0%)	35 (87.5%)	35 (92.1%)	58 (92.1%)	54 (85.7%)
Education (highest grade passed 1-12) HHH, n (%)	64 (82.1%)	70 (76.9%)	34 (85.0%)	38 (100.0%)	36 (58.1%)	46 (73.0%)
Unemployed, n (%)	50 (55.0%)	39 (50.0%)	31 (77.5%)	20 (52.6%)	35 (55.6%)	29 (46.8%)
Unemployed HHH, n (%)	46 (50.6%)	35 (44.9%)	17 (42.5%)	17 (44.7%)	25 (39.7%)	38 (61.3%)
Never married/single, n (%)	47 (51.7%)	42 (53.9%)	34 (85.0%)	36 (94.7%)	39 (61.9%)	44 (69.9%)
Mean adults in HH (std dev)	2.52 (1.6	2.26 (1.3)	2.93 (1.1)	2.5 (1.5)	2.32 (1.9)	4.27 (2.3)
Mean children in HH (std dev)	1.26 (1.6)	0.89 (1.2)	1.48 (1.5)	2.18 (2.1)	1.76 (1.7)	3.37 (3.0)

385

386 HHH head of household

387 Table 2: Direct and indirect patient costs (USD$, year 2020) during treatment (from patient cost survey)

	Gauteng		KwaZulu-Natal		Western Cape	
	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6
	Intervention	Control	Intervention	Control	Intervention	Control
N	91	78	40	38	61	61
	Arithmetic mean (% of total cost)	Arithmetic mean (% of total cost)	Arithmetic mean (% of total cost)	Arithmetic mean (% of total cost)	Arithmetic mean (% of total cost)	Arithmetic mean (% of total cost)
Direct medical costs						
Clinic fees	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)
Medicines	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)
Direct non-medical costs						
Transport (return) to clinic	4.47 (3.8%)	3.23 (3.5%)	3.58 (6.5%)	3.04 (2.7%)	3.03 (7.8%)	1.58 (2.2%)
Childcare whilst attending the clinic	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	4.86 (13.5%)	0.00 (0.0%)	0.00 (0.0%)
Accommodation whilst attending the clinic	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)
Food whilst attending the clinic	0.42 (0.4%)	0.71 (0.8%)	1.34 (2.4%)	2.31 (6.4%)	0.67 (1.7%)	0.00 (0.0%)
Special food – during treatment	30.58 (25.9%)	24.39 (26.5%)	15.49 (28.0%)	20.86 (58.1%)	13.16 (33.8%)	14.99 (20.5%)
Phoning whilst attending the clinic	0.10 (0.1%)	0.19 (0.2%)	0.25 (0.4%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)
Accompanying adult whilst attending the clinic	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)	0.00 (0.0%)
Direct costs: sub-total	**35.57 (30.2%)**	**28.51 (31.0%)**	**20.66 (37.3%)**	**31.06 (86.5%)**	**16.86 (43.3%)**	**16.56 (22.6%)**
Indirect costs						
Foregone income	82.37 (69.8%)	63.43 (69.0%)	34.66 (62.7%)	4.86 (13.5%)	22.12 (56.7%)	56.68 (77.4%)
Total costs per PWTB	**117.94 (100%)**	**91.94 (100%)**	**55.32 (100%)**	**35.92 (100%)**	**38.98 (100%)**	**73.25 (100%)**

388

389 **Table 3: Clinic visits per site for all trial participants**

Visit	Gauteng		KwaZulu-Natal		Western Cape	
	Site 1 (n=157)	Site 2 (n=109)	Site 3 (n=95)	Site 4 (n=170)	Site 5 (n=171)	Site 6 (n=170)
	Intervention	Control	Intervention	Control	Intervention	Control
Visit 1_Enrolment*	157	116	97	170	233	217
Visit 2_Month 1	126	79	27	22	114	133
Visit 3_Month 2	108	65	22	10	108	107
Visit 4_Month 3	91	55	19	7	94	88
Visit 5_Month 4	81	50	24	6	65	66
Visit 6_Month 5	67	51	24	2	66	67
Visit 7_Month 6	75	57	37	6	87	57
Total visits*	**705**	**473**	**250**	**223**	**767**	**735**
Mean visits per participant (std dev)	**3.45** (2.01)	**3.48** (2.09)	**3.26** (2.30)	**1.60** (1.35)	**3.31** (2.03)	**3.11** (1.97)
Number of phone calls per site	**299**	**0**	**162**	**0**	**141**	**0**
Number of home visits per site	**41**	**0**	**8**	**0**	**114**	

390 *Includes screening failures

391 *Visits counted if PWTB seen by study staff

392 Table 4: Key parameters and assumptions

393

Parameter	Value	Source
Drug dispenser sim card	$0.91	Wisepill invoice
Airtime per phone line for study staff (over a 6 month period)	$40.10	Trial logs
Airtime for the dispenser module	$1.03	Wisepill invoice
Number of SMS (Short Message Service) reminders for missed doses over 6 months (per participant)	Site 1= 48 Site 3= 50 Site 5= 64	RCT logs and invoices
Cost per SMS	$0.03	Wisepill invoice
Healthcare worker wage per hour (adherence monitoring)	$8.11	Financial records
Cost per hour for data management staff	$14.82	Financial records
Number of days data management support provided per site (6 months)	Site 1= 8 Site 3= 6 Site 5= 8	Interview
Monthly data & phone plans used (over 6 months) per site	$46.69 - $82.67	Interview
Number of phone calls made for non-adherence per site	Site 1= 299 Site 3= 162 Site 5= 141	RCT logs
Average study staff time per call for non-adherence (minutes)	10	Interview
Number of home visits made for non-adherence (including repeat visits) per site	Site 1= 41 Site 3= 8 Site 5= 114	RCT logs
Average time per home visit including travel (minutes)	82.38	Time and Motion
Amount of time for training (total minutes) per study staff per site	480	Interview
Working days per year	251	Assumption
Working minutes per day	480	Assumption

394

395

396 Table 5: Health system cost per patient (USD$, year 2020) using amedication monitor (Wisepill) and differentiated care approach – by
397 site
398

Cost component ($)	Gauteng		Incremental cost (%)*	KwaZulu-Natal		Incremental cost (%) *	Western Cape		Incremental Cost (%) *
	Site 1 Intervention	Site 2 Control		Site 3 Intervention	Site 4 Control		Site 5 Intervention	Site 6 Control	
Medication monitors and accessories (battery, modules and dispenser SIM card)	24.38	0.00	24.38 (57.0%)	24.38	0.00	24.38 (42.0%)	24.38	0.00	24.38 (64.0%)
Phone and accessories for study staff	0.31	0.00	0.31 (1.0%)	0.52	0.00	0.52 (1.0%)	0.29	0.00	0.29 (1.0%)
Wisepill platform hosting, support and reminders	3.70	0.00	3.7 (9.0%)	3.75	0.00	3.75 (7.0%)	4.2	0.00	4.2 (11.0%)
Adherence monitoring using Wisepill platform	3.16	0.00	3.16 (7.0%)	1.63	0.00	1.63 (3.0%)	2.58	0.00	2.58 (7.0%)
Data management and technical support	7.41	0.00	7.41 (17.0%)	7.93	0.00	7.93 (14.0%)	6.38	0.00	6.38 (17.0%)
Differentiated care approach for non-adherence (Phone calls)	2.61	0.00	2.61 (6.0%)	2.37	0.00	2.37 (4.0%)	1.15	0.00	1.15 (3.0%)
Differentiated care approach for non-adherence (Home visits)	5.99	0.00	5.99 (14.0%)	1.09	0.00	1.09 (2.0%)	8.64	0.00	8.64 (23.0%)
DAT training for study staff (trainee) – Annualised Cost	0.17	0.00	0.17 (0.0%)	0.24	0.00	0.24 (0.0%)	0.13	0.00	0.13 (0.0%)
Additional training costs (trainer) – Annualised Cost	0.13	0.00	0.13 (0.0%)	0.21	0.00	0.21 (0.0%)	0.12	0.00	0.12 (0.0%)
Clinic costs (Staff time -TB nurse) **	36.68	39.28	-2.6 (-6.0%)	24.27	8.97	15.3 (27%)	17.08	26.96	-9.88 (-26.0%)
TOTAL	81.93	39.28	**42.65**	66.39	8.97	**57.42**	64.95	26.96	**37.99**

399 *Incremental cost = cost of the intervention – cost of the control within each province. % refers to the percentage of the total incremental/decremental cost.
400 **Staff time cost (TB nurse) = average time per patient x cost per minute

401 **Table 6: Sensitivity analyses considering either device re-use, alternative cadre or**
402 **platform hosting for all PWTB – Cost per patient (USD$, year 2020)**
403

Input		Gauteng		KwaZulu-Natal		Western Cape	
		Site 1	Site 2	Site 3	Site 4	Site 5	Site 6
		Intervention	Control	Intervention	Control	Intervention	Control
Device re-use	Total	65.67	39.28	50.14	8.97	48.69	48.69
	Incremental cost of intervention*	26.40		41.17		21.73	
Alternative cadre	Total	84.76	39.28	67.85	8.97	67.26	26.96
	Incremental cost of intervention*	45.49		58.89		40.30	
Platform hosting (all PWTB)	Total	79.87	39.28	64.33	8.97	62.89	26.96
	Incremental cost of intervention*	40.59		55.36		35.93	

404 *Incremental cost of intervention = cost of the intervention – cost of the control
405

406

407 **Table 7: Incremental cost-effectiveness ratio (ICER) of DAT intervention (medication**
408 **monitor and differentiated care approach) versus standard of care**

	Intervention	Control	Incremental difference	ICER
Study population	1306	1278		
Health system cost[1]	$ 71.09	$ 25.07		
Patient cost[1]	$ 70.75	$ 67.04		
Societal cost[1]	$ 141.84	$ 92.11		
Total cost[2]	$ 185,243.04	$ 117,712.32	$ 67,530.72	166.33
Effectiveness[3]	1056	650	406	

409 [1] arithmetic mean of costs across the three provinces, by study arm
410 [2] societal cost multiplied by the study population
411 [3] effectiveness is calculated as the number of participants per arm who satisfied the primary outcome of ≥80%
412 adherence
413 ICER incremental cost-effectiveness ratio (incremental difference in total cost divided by the incremental
414 difference in the number of participants satisfying the primary outcome)
415

Ethics approval and consent to participate

The parent study received ethics approval from the three district and provincial ethics committees where the trial sites were located. This costing study was approved by the Human Research Ethics Committee (HREC) of the University of Witwatersrand (Ref 180705) and the University of Cape Town (Ref 452/2018), as well as, from the London School of Hygiene & Tropical Medicine (Ref 16107). We obtained written informed consent for study participation from all participants. Participants were not reimbursed.

Availability of data and material

No additional data available

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

CRT	Cluster-randomized trial
DCA	Differentiated Care Approach
DS-TB	Drug-sensitive TB
DATs	Digital Adherence Technologies
PHC	Primary Health Care
PWTB	People With TB
SA	South Africa
SMS	Short Message Service
SoC	Standard of Care
TB	Tuberculosis

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CHAPTER 7: SUMMARY, DISCUSSIONS AND CONCLUSIONS

7.1 Summary and discussion of the main findings

To accurately measure adherence to TB treatment there is the need for improved methods such as digital technologies which do not rely solely on clinic or home visits. Furthermore, technologies that remotely monitor adherence in real time and alert providers regarding those PWTB who may need support in adhering to treatment can help reduce transmission of TB within communities. This PhD has sought to fill the knowledge gap on the value of digital technologies through evaluating the feasibility, acceptability, and cost-effectiveness of an adherence monitoring system. By use of a mixed methods approach utilizing both qualitative and quantitative methods this PhD has yielded manuscripts which have been published in international journals and findings which have been presented at both local and international conferences.

The PhD manuscripts are premised on the results of the TB MATE trial as it is necessary to first evaluate effectiveness of an intervention before looking at other factors such as feasibility, acceptability and cost-effectiveness. TB MATE trial showed that adherence to TB treatment improved in the intervention arm as compared to the control arm (81% vs 50.8%), though the treatment outcomes did not show any improvement [62]. This result was difficult to understand and interpret since WHO measures treatment success rather than adherence. Policy makers are often more interested in treatment success when making decisions on whether they are willing to pay for an intervention to be scaled-up nationally. Nonetheless, the effect on adherence is important and perhaps these technologies need additional

interventions to improve treatment outcomes [62]. The elements that are evaluated in this PhD namely feasibility, acceptability and cost-effectiveness will also give an understanding of what additional interventions could help improve treatment outcomes. I will discuss the main findings of each of the manuscripts in turn.

The first manuscript addressed the objective on the feasibility of implementing Wisepill evriMED device and differentiated care from a stakeholder perspective. As previously mentioned in chapter 4, the qualitative study has shown that Wisepill evriMED device and the differentiated model of care is feasible to implement within the existing health system. Providers felt the intervention could be easily integrated into the health system and it would assist them in monitoring and supporting adherence to treatment for PWTB and also those with other chronic conditions. For the adherence system to operate optimally, there is a need to improve upon the technical glitches such as network connectivity which is important especially if the intervention is scaled up to rural areas.

The challenges of implementing Wisepill evriMED device and differentiated care which are described in the first manuscript on feasibility are similar to those found in the DATs study done in the Philippines as part of the Adherence Support Coalition to End TB (ASCENT) trial where poor network connection was cited as a reason for taking TB treatment without using the smart pillbox [30]. In the first manuscript we also found that poor network connection could also result in the system not recording box opening in real time, yet the PWTB had timeously opened their device as instructed. These system issues sometimes have a negative impact on the patient-provider relationship since PWTB tend to distrust healthcare

providers who initiate unnecessary sms's, phone calls or home visits. Another issue that may undermine the adherence monitoring system and create distrust is when the PWTB open the medication monitor and not ingest any of the pills as some providers on the TB MATE study feared. The solution to this problem, as suggested by stakeholders who were interviewed, may be through constant education to the PWTB so that they can understand the importance of taking their treatment on time, every day, for the full treatment duration, even without anyone having to monitor them. This solution has also been cited by the authors of the ASCENT trials conducted in Ethiopia, the Philippines, South Africa and Tanzania where they indicate that interventions aimed at improving medication adherence should follow a holistic approach that goes beyond monitoring pillbox openings [30]. Instead, they should address individual behavioural and psychosocial factors may be necessary for enhanced effectiveness [30].

The second manuscript addressed the objective on the acceptability of implementing Wisepill evriMED device and differentiated care from a PWTB perspective. As briefly mentioned in chapter 5, this manuscript has shown that Wisepill evriMED device and the differentiated model of care is acceptable to PWTB as it acts as a reminder to take medication especially for those who do not have family support. Even those PWTB who had family support acknowledged that it felt good knowing that there were other people looking out for their health besides their family and even attributed their healing to the device. However, there were some PWTB who perceived the medication monitor as creating stigma due to its current design and hence they chose to leave it at home when they travelled or went to work. Some PWTB across gender and adherence history felt that the monitor was large, and the alarm

drew attention to their TB status, potentially causing embarrassment and stigma. Due to perceptions of stigma, PWTB adapted the intervention by taking pills out of the monitor and leaving it at home so someone else could track usage for them while they used alternative reminders such as cell phones to take their medication. This finding is similar to the ASCENT trial where fear of stigma related to taking TB medication using the DATs resulted in participants leaving their pillbox behind when traveling or going to work [30]. However, one can argue that the monitor created a change in PWTBs behaviour and caused them to use alternative reminders which may have not been the case had the monitor not existed. One limitation of the acceptability study is that parents and caregivers of children under the age of 18 years who were part of the CRT were not included in the qualitative study. It would have been interesting to understand their views on the medication monitor and DCA and the possibility of any associative stigma they may have perceived or experienced as a result of caring for a child with TB.

The third manuscript showed that the cost of achieving an additional adherent PWTB was estimated at $166.33. This cost can be considered relatively affordable given that there are only about 270 000 PWTB (drug sensitive) in the whole of South Africa and if we allowed for an uptake of 85% then only 229 500 PWTB would require a monitor, meaning that the total cost for the country would be around $38m [63]. The cost of TB treatment in SA is about $107 per PWTB and adding $166.33 to improve adherence to treatment and avoid treatment failure can be considered worth it [64]

We also indicated ways that the costs could be reduced. As highlighted in chapter 6, the cost of medication monitors and DCA can be considered a cost-effective option for scale-up given that the intervention had a significant impact on adherence with effectiveness estimated at 81% and 50.8% in the intervention and control arms respectively. The cost of the medication monitors can be reduced through other ways such as negotiating a lower cost for monitors with manufacturers and by giving the monitor to fewer people such as those PWTB who showed relatively good adherence as measured by missing one dose only. Another suggestion would be to give the adherent PWTB the monitor in the intensive phase only and not during the continuation phase of treatment which would help reduce the costs to the health system. The monitor can also be used to help reduce the clinic visits for the adherent PWTB as monitoring can take place from a central location without the need for unnecessary clinic visits, helping to reduce health systems costs. A reduced number of clinic visits would also help in decreasing patient costs that are incurred due to PWTB missing work to attend clinic visits. In the third manuscript, productivity losses in terms of foregone income were found to be one of the biggest drivers of patient costs ranging between 13.5% - 77.4% of total costs to PWTB.

There are some strengths and also some limitations to this PhD study. A primary strength is that this is the first large study conducted in the South African setting on medication monitors and a DCA to improve adherence to TB treatment. Most studies of a similar nature have been pilot studies and have not measured or explored all three aspects of feasibility, acceptability and cost-effectiveness of the medication monitor and DCA[15, 23-25]. Secondly, this PhD study was conducted in three geographically diverse provinces of SA which allowed us to

understand the feasibility of the intervention in different settings which allows us to generalize the findings nationally. Thirdly, we included the experiences of both providers and PWTB in helping us understand if the intervention was acceptable and what aspects we would need to consider from both perspectives when scaling up. Fourthly, the cost-effectiveness component of the study gave us insights into what costs would be incurred by the health systems and the PWTB and how best to reduce these costs including suggestions of which groups to prioritize when scaling up as was shown through the sensitivity analysis.

There were also some limitations encountered during the course of this PhD. Firstly, using the monitor to measure adherence can under-estimate adherence if PWTB use other forms of reminders such as cell phones, or over-estimate adherence if PWTB keep other tablets in the monitor causing them to open the device more frequently. Secondly, training costs considered in the cost-effectiveness analysis were once-off, however, once the intervention is scaled-up, stakeholders suggested continuous training to healthcare providers to ensure that the intervention is sustained. Thirdly, the cost-effectiveness analysis was based on adherence only and long-term impact on transmission and on averting TB cases is not known. To estimate the long-term impact on transmission would be difficult as the impact of adherence on transmission is not known. Fourthly, pre-treatment costs were captured only after two months and hence the costs may have been influenced by recall bias. Finally, doing the study in SA only can be considered a limitation since the findings cannot be generalized to other African countries given that the SoC may be different, and DATs are more likely to be cost-effective where there is DOTs implementation as the SoC. Also, the costs such as salary scales are different in the African countries making the transferability of results difficult.

7.2 Theoretical assessment of equity

Wisepill evriMED device allows for more equity or fairness in access since the requirements are more lenient e.g. a feature phone and not a smart phone like other methods like VDOT require. This means that those of lower socio-economic status also have access to this intervention. However, those of a lower socio-economic status may live in smaller homes and may lack privacy to use the monitor in the presence of family members who they may not have disclosed their TB diagnosis to. This means that the allocation of the monitor would need to be preceded with sufficient education and counselling so as to encourage the PWTB to disclose their TB status to their family members thus making the use of the monitor less burdensome. This also applies to those who fear discrimination in the workplace due to inadvertent disclosure of their TB status as a consequence of using the monitor in public. These individuals would need to select a time for their reminders when they know they will be home with their family or other household members who know their status and are less likely to treat them differently.

Considerations of the criteria that can be used to make a decision on who should be given the medication monitor can be based on risk factors associated with adherence to TB treatment where we find that living with HIV (regardless of ART status) and being of a younger age are associated with poor adherence (less than 80%) [65]. Also, in a sub-group analysis of the TB MATE CRT, the intervention reduced the unfavourable outcomes (loss to follow-up and deaths) in some sub-cohorts e.g. females which is another group that could be prioritized for the monitor and DCA since greater benefit was shown [62]. Therefore, PWTB who are co-infected with HIV, are females and are of a younger age is a group that can be prioritized for

the medication monitor. When scaling-up, there are other groups which careful consideration needs to be made such as drug users, homeless people, and seasonal farm workers in the Western Cape.

7.3 Policy implications

Monitoring TB treatment adherence using DATs and DCA was found to be acceptable, feasible and cost-effective and should be considered for scale-up. Societal costs will underpin the decision-making process and ways to reduce these should be prioritized to maximize scale-up. Patient insights into their perceptions of stigma should be assessed on an on-going basis as these influence the successful adoption of DATs and DCA. Providers should be trained on how to support PWTB take ownership of their treatment journey to reduce their perceptions of stigma. DATs can help address certain reasons for non-adherence like forgetfulness but not issues like lack of food, side effects etc. which prevent PWTB from taking their treatment. Incorporating social protection as a way of addressing patient costs like food and transport which serve as barriers to adherence to treatment can help promote access to DATs and help achieve universal health care for all. National TB Programs (NTPs) could use the intervention to reduce the number of visits to the facility by remotely monitoring and supporting people taking TB treatment and by doing so reduce transport costs and improve financial risk protection or catastrophic costs for PWTB.

NTPs should be aware that giving the device to just a few may not reduce the cost per patient since fixed costs of the monitoring system will be shared by just a few patients. One would need to weigh this against the reduction of recurrent costs of the device.

Another disadvantage of giving the device to too few people is that if staff only use the system a few times a year, then habit formation is limited for the system users and they may forget how to operate the system efficiently.

Due to limited resources, the medication monitor and DCA should initially be used for those with PWTB who are co-infected with HIV, are females and are of a younger age. Over time, the monitor should also be given to patients with DR-TB and other chronic conditions so as to reduce the cost per patient and also to reduce any stigma associated to having only a very specific group utilize the monitor.

7.4 Conclusions

Achieving people-centred TB care, including the introduction of DATs, will require that TB programmes incorporate insights of both PWTB and providers in order to maximize their adoption and effectiveness. Perceptions of stigma motivate PWTB to adapt use of medication monitors to their lifestyle and providers need to have an understanding of these adaptations so as to scale-up the intervention in a sustainable manner. Various ways are available to help reduce the costs of the medication monitor and DCA to the health system. The intervention can be considered as cost-effective for scale-up in SA since it helps improve adherence to treatment. Adherence would help reduce recurrence and drug-resistant TB and thus reduce costs for the health system and the patient. Digital adherence tools are a good example of why it's important to measure costs borne by both PWTB and health systems as well as insights from PWTB and providers as these factors all vary by context and influence the success of an intervention.

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APPENDICES

Appendix A: Results from the cluster randomised trial

Introduction

This was a quantitative paper that showed the cluster randomised trial outcomes of implementing Wisepill evriMED device and the differentiated model of care in three provinces of South Africa.

Paper 4: Treatment adherence and clinical outcomes amongst drug-susceptible TB persons using medication monitor and differentiated care approach in South Africa: results from a cluster randomised trial

Treatment adherence and clinical outcomes amongst in people with drug-susceptible tuberculosis using medication monitor and differentiated care approach compared with standard of care in South Africa: a cluster randomized trial

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Summary

Background Poor treatment adherence contributes to lower treatment completion and higher loss to follow-up among people with tuberculosis (PWTB). Medication monitors have shown some evidence of improved adherence.

Methods We conducted a cluster randomised trial in 18 primary health clinics in South Africa between May 2019–February 2022. Persons (aged ≥ 2 years) with drug-sensitive tuberculosis (DS-TB) were enrolled. All participants were provided with monitors which were silent in the standard of care (SoC) arm. In the intervention arm, weekly adherence reports were reviewed and participants received intensified support as appropriate (text, phone call, home visit, motivational counselling). The primary outcome was adherence, which was calculated as days box was opened (proxy for drug taken)/total expected treatment days as a binary variable (<80% versus ≥80%). Analysis took into account clustered design. The trial was registered with the Pan African Trial Registry PACTR201902681157 72.

Findings We enrolled 2727 participants (38% women, median age 36 (IQR 27–45 years), of whom 2584 had available adherence data. The primary outcome (measured as ≥80% adherence) was higher in intervention versus SoC arm (81.0% versus 50.8%, adjusted risk ratio (ARR) 1.51 (1.36–1.66). Similarly, overall percentage adherence was higher in intervention versus SoC arm (88.5% versus 69.7%, adjusted risk difference 16.8% (13.3%–20.4%)).

Interpretation People with DS-TB had improved treatment adherence in the intervention arm. We believe the effect on adherence is important and warrants continued use and evaluation of these technologies.

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Keywords: Medication monitors; Differentiated care approach; Treatment outcomes; Adherence; Tuberculosis; Recurrence

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Research in context

Evidence before this study

We searched Medline and Embase in June 2018 for papers published from Jan 1, 2000, to May 1, 2019, with no language restrictions, using the terms ("digital pill box*" OR "smart pill box*") AND "TB" OR "tuberculosis". We found one systematic review of sixteen randomized control trials (RCTs) of digital adherence tools to improve adherence to tuberculosis (TB) with only two including medication monitors. One study on medication monitors showed reduced missed doses while the other showed no differences. Prior to our study, the only important evidence came from one large trial conducted in China, completed in 2012, included 4292 new pulmonary TB participants were enrolled across the 36 clusters. The adherence outcome of at least 20% of doses missed (as measured by box-opening), was lower in the in the medication monitor arms. The study was not powered for treatment outcomes, and it was found that the differentiated care aspect of the intervention was not well implemented. The only study for South Africa, was a study showed high acceptability of medication monitors has previously been described in people with drug-resistant TB. However, no study had been conducted among people with drug-sensitive TB (DS-TB) and no study had measured treatment outcomes.

Added value of this study

Our study was a large study done in routine clinics in three distinct settings in South Africa and is one of few studies that evaluated medication monitors using a cluster-randomised approach and that included follow up for recurrence. The use of medication monitors and differentiated care showed an improvement in adherence although there was no significant difference in unfavourable outcome in people with DS-TB, despite a trend to improvement in the intervention arm. There was an impact of adherence on unfavourable outcomes in some sub-cohorts e.g., women which indicates that this is potentially a particularly important intervention and should be evaluated further.

Implications of all the available evidence

We are not able to recommend medication monitors across the board for people with drug-sensitive TB at this point. Our study supports existing literature indicating improved adherence with medication monitors but failure to show a change in treatment outcomes. It may be that there needs to introduce additional interventions to improve treatment outcomes.

Introduction

Globally, tuberculosis (TB) treatment success rates among new and relapse cases have not improved over the last ten years.[1] Among the 7.5 million people with TB in 2023, almost 900,000 individuals were not successfully treated.[1] Poor treatment adherence contributes to lower treatment completion rates and to higher rates of loss to follow-up among people with TB (PWTB)[2,3] and has been associated with increased relapse of TB.[4] In a patient-level pooled analysis of treatment shortening trials, poor medication adherence (≤90%) was associated with increased risk of poor treatment outcomes and recurrence.[5]

Digital adherence technologies (DAT) are increasingly used to improve medication adherence[6] and treatment outcomes.[7] Medication monitors in particular, if effective and accurate, may potentially reduce the need for clinic visits allowing for monitoring of adherence patterns from a central location.[8] The newer adherence devices enable real-time monitoring of pill-taking, generating more detailed adherence histories which can be actioned more quickly, and allowing for a differentiated use of limited human resources for managing challenging PWTB. The World Health Organisation (WHO) updated treatment guidelines currently includes a conditional recommendation, with very low certainty of evidence, to offer medication monitors and tracers (such as mobile phone short message service (SMS)) for TB treatment adherence support.[9]

Previous evidence for effectiveness of digital monitors mainly come from two large trials conducted in China. The first trial, which was completed in 2012 and included 4292 new pulmonary TB participants across the 36 clusters, showed that poor adherence (measured as at least 20% of doses missed, as measured by box-opening), was lower in the in the medication monitor arms.[8] In the more recent Chinese trial, the medication monitor intervention had no effect on unfavourable outcomes (adjusted risk ratio 1.01, 95% CI 0.73–1.40), but non-adherence was reduced by 57–64% in the intervention group compared with the control group,[10] although there were concerns about a failure to change patient management following identification of treatment non-adherence at monthly reviews. Other evidence from Ethiopia, includes one individually randomised trial of 337 individuals which showed superior adherence (using different measures), but no change on smear conversion, among participants assigned to monitor-observed self-administered therapy when compared with the standard in-person facility-administered DOT.[11] More recently published smaller studies from Tibet (n = 278) and Peru (n = 106), indicate improved treatment outcomes with use of digital[12,13] with improved adherence in one (Tibet) and no change in adherence in the other (Peru). The Tibet study did include a more comprehensive package of interventions with electronic monitors, family treatment supporters and improved communication through a

linked smartphone app. Thus to date, although some smaller programmes and with more intensive adhrence support have shown some benefit, large programme implementation of DAT had failed to show consistent effect on treatment outcomes.

South Africa, a country with a high estimated TB incidence rate (468/100,000 population), reported treatment success rates of 79% among new and relapse PWTB, 79% among HIV-positive PWTB and 62% among people on rifampicin resistance TB treatment,[1] falling short of targets of 90% treatment success of all forms of TB in the Global Plan to End TB (2023–2030).[14] The acceptability of medication monitors has previously been described in people with drug-resistant TB in South Africa.[15] However, no study had been conducted using adherence monitors among people with drug-sensitive TB (DS-TB). In addition, no study has evaluated treatment outcomes, including recurrence, in patients using the real-time medication monitors which allow for differentiated care in South Africa. We conducted a pragmatic trial with the aim to evaluate an adherence monitoring system with a differentiated response to patient care, among people with DS-TB in three provinces in South Africa.

Methods

The study was a parallel cluster-randomised trial conducted across 18 primary health care facilities in three provinces in South Africa (Ekurhuleni district in Gauteng, Klipfontein and Mitchell's Plain districts in Western Cape, and eThekwini district in Kwa-Zulu Natal) and was described fully previously.[16] Clusters were public health clinics with at least 200 TB registrations in 2017 and included six clinics per province. Adult HIV prevalence in the general population was 18.2% in Kwa-Zulu Natal, 12.5% in Gauteng and 8.9% in Western Cape province.[17] Standard of Care (SoC) in South Africa was mostly self-administered treatment with directly observed treatment provided to people thought to have risk factors for poor adherence (e.g., homeless, substance abuse history etc). In the Western Cape province, it was mostly self-administered treatment except for the first two weeks of treatment that were directly observed.

The study enrolled adults aged ≥ 18 years and children aged 2–17 years with clinically or microbiologically diagnosed DS-TB, satisfying inclusion criteria of having initiated TB treatment within the last 7 days at the time of enrolment; willing to use the medication monitor as directed; agreeing to be followed-up with text messaging; phone calls and home visits; living within the study catchment area; and willing to inform the study team of any change of address during the treatment as well as follow-up period. Participants (or caregivers in the case of children) were also required to have access to a mobile phone and no phones were given to participants. Participants were excluded if: they were diagnosed with drug-resistant TB; they were not fluent in the languages in which the informed consent was provided or study members were not able to communicate; those who do not have access to or were not able to use a mobile phone or to read SMS text messages; people unable to use the device after training, people who expect to leave the study area, people taking part in the other investigational product or device trials related to TB and/or lung diseases. The inclusion criteria for initiating TB treatment were later revised to within 14 days as patients that were initiated on TB treatment in hospitals were referred to continue with their treatment in primary health facilities having been on treatment for more than 7 days.

Randomisation and masking

Clusters were randomised 1:1 to intervention or SoC arm using restriction to ensure a difference in clinics per arm in each of province of no more than one. Randomisation allocation sequences were done by the study statistician using STATA v16. Following the randomisation but before participant enrolment had started, two clinics from the same province, one in each arm, were withdrawn due to ongoing TB studies. The two clinics were replaced by another two clinics in the same province and were randomly allocated to the intervention and control arm. Research staff were placed at each of the 18 clusters to enrol participants into the study. There was no masking of the intervention. Both providers and participants were aware of the randomisation.

Procedures

Participants enrolled from clinics in the intervention arm received a differentiated care adherence package. The package included standard patient education and provision of the Wisepill EvriMED medication monitor, wherein treatment blister packs were placed, and which were programmed to have daily visual or audio alerts for treatment intake and monthly reminders for treatment refills. If a PWTB missed one dose, they received an automated SMS stating, 'Please remember to take your medication'. A second or third missed dose in a week, required research staff to initiate a phone call to the participant, and four or more missed doses in a week required a home visit. Research staff were provided with scripts to use for the phone calls and home visits. If four or more doses were repeatedly missed, motivational counselling was initiated. When participants went to the clinic for their routine monthly dispensing visit, the research staff showed the participant their own data and discussed their medication adherence history.

Participants enrolled from clinics in the SoC arm received counselling regarding their TB treatment and were given a return date for collection of repeat medication in 30 days. Participants were also provided with the medication monitor wherein treatment blisters packs were placed and educated on its use by the

research staff. The medication monitor did not provide any visual or audio reminders for intakes or refills but recorded data on box opening in real-time just as in the intervention arm. In contrast to the intervention clinic participants, data collected on the system were not reviewed during routine monthly follow-up visits by research staff or participants. In both arms, the medication monitor transmitted a daily "heartbeat" signal to the system to indicate that it is working properly. If not working, health care workers did assist participants in both arms to ensure the monitor was functioning and able to send signals.

For study visits, participants in both arms were followed up by the research team passively each month during TB treatment. As per usual care, facility staff documented end of treatment outcomes without any interference by our research staff.

Following the end of treatment, participants in both arms who had cured or completed treatment were followed-up every three months in person (except during the COVID-19 lockdown period) for 12 months. During this follow-up period, participants were determined as having "died" if research staff were informed by their contacts as having died or "lost to follow-up" if they could not be found after multiple phone call or home visits attempts where possible to them or their contacts. At each follow-up visit, TB symptom screening was performed and, if symptomatic, a sputum sample for Mycobacteria Growth Indicator Tube (MGIT) culture and Xpert MTB/Rif (as per routine) was collected. All participants were requested to provide a single sputum specimen for MGIT culture testing at 6 months from enrolment and 12 months post TB treatment completion (18 months from enrolment), regardless of symptoms. Participants were reimbursed ZAR 50 (approximately US$3) for travel costs for each visit after the end of treatment as these were deemed research visits.

Outcomes

Outcomes were described in the protocol prior to start. The primary study endpoint was adherence to TB medication, which was measured as a binary outcome of percentage adherence ≥80% over the whole period, as measured by box opening. For those lost to follow-up during treatment, we assumed no drug intake (100% non-adherence) for the period from the date of last contact to the date of scheduled treatment completion. TB medication adherence was also calculated as a continuous variable, by arm, defined as the percentage adherence over the entire treatment period.

Secondary study endpoints included poor outcome at the end of treatment and unfavourable outcomes at 18 months post enrolment. Poor end of treatment outcome was defined as death, lost to follow up, treatment failure (including positive culture on the six-month sputum) and diagnosis of rifampicin resistant TB. Transfer outs and where an outcome was not documented (and no negative culture at end of treatment) were coded as not assessable. Unfavourable outcome at 18 months after enrolment included: on-treatment lost to follow up, death, treatment failure, diagnosis of multiple drug resistant TB (MDR-TB) and treatment recurrence. Treatment recurrence was defined as a participant having a positive TB culture result (either as part of the trial or in routine care) or restart of TB treatment at any time during the 12 months follow-up period post TB treatment completion. All analyses were conducted using the intent to treat population, defined as all participants enrolled on the study, excluding those with diagnosis changed to not TB or MDR TB, those incarcerated in follow-up and those who no longer wished to participate. Multiple imputation (25 imputations) was conducted for individuals who had cured or completed treatment, had not met the recurrence endpoint and who were not seen at 18 months (either due to lost to follow-up or death). Two sensitivity analyses were also done: 1) participants who had a treatment outcome of cured or completed treatment, but who had been on treatment for >10 months (280 days), defined as having as poor end of treatment outcome; and 2) participants who had a treatment outcome of success or completed treatment, but who had died between end of treatment and 18 months, defined as an unfavourable outcome.

Statistics

Sample size calculations were conducted accounting for the clustered design and assumed a harmonic mean of 145 participants/cluster, nine clusters per arm and a two-sided type I error of 5%. For the primary outcome (adherence) we assumed the percentage with adherence less than 80% in the SoC arm of 30% and coefficient of variation of 0.25, had 90% power to detect a 40% relative reduction in the endpoint in the intervention arm. For a successful outcome at the end of treatment, we assumed 80% successful outcome in the SoC arm and a coefficient of variation of 0.06, we had 90% power to detect an increase to 90%. For unfavourable outcome 18 months after enrolment, we assumed 13–20% in the SoC arm and a coefficient of variation of 0.25, we had at least 80% power to detect a 40% relative reduction in the intervention arm. Allowing for some clinics to enrol more than others, we did allow enrolment of up to 170 per clinic. The STATA "clustersampsi" command was used for the sample size calculations.

Analysis was conducted at the cluster-level due to the small number of clusters.[18] For each cluster, the proportion of participants with <80% adherence was measured. Our main effect estimate is a risk ratio based on the natural logarithm-transformed risks, compared by study arm across clusters using a t-test. For all binary outcomes, we reported by study arm the overall risk, ignoring clustering, and the geometric means of cluster-level risks. We also conducted an adjusted analysis for the intervention effect, adjusting for imbalances of

individual-level variables at baseline, using a two-stage approach. Using logistic regression, the expected outcome for each individual was calculated, adjusting for baseline imbalances and summed at the cluster-level. The log of cluster-level residual (expected number of outcomes with the observed number of outcomes) was compared by study arm using a t-test. Risk differences and associated 95% confidence intervals by study arm were reported, based on untransformed cluster-level risks. Prespecified subgroup analyses were conducted without control of the overall type I error rate. All analyses were conducted in STATA v16 using the clan command.[19] No interim analysis was performed.

For fidelity of the intervention, we opted to measure the required phone calls (since home visits were not done during COVID time) and how many were attempted and the number of circumstances where the person was successfully contacted.

Ethics

Written informed consent was obtained from all adults. For children under 18 years, caregivers gave informed consent and in children aged 7–17 years old informed assent was also obtained. The trial obtained approval from Wits Human Research Committee (Ref 180,705), Johannesburg, South Africa; University of Cape Town Human Ethics Research Committee (Ref 452/2018), Cape Town, South Africa; and the London School of Hygiene & Tropical Medicine (Ref 16,107), London, United Kingdom. The study also obtained approval from the three district health departments: eThekwini, Ekurhuleni, and City of Cape Town. The trial was registered with the Pan African Trial Registry PACTR201902681157721, registered on 11 February 2019.

Role of funding source

Funders did not play a part in the design of the study or the decision to submit the manuscript for publication.

Results

From 17 May 2019 to 31 December 2020, we enrolled 2727 participants (38%, 983 women; median age 36 years, Interquartile range 27–45 years) from 18 facilities (10 community health centres and 8 primary health clinics): 19 (0.7%) participants were incorrect enrolments and 51 (1.9%) withdrew their participation in the study, leaving 2657 individuals (Fig. 1). The COVID pandemic and subsequent restrictions imposed interrupted enrolment and reduced home visits. Recruitment was paused from March–June 2020. In addition, home visits were replaced with phone calls between March and July and also in other lockdown periods following July 2020 depending on the levels of restrictions. Facilities closures days varied between 0 and 22 days from March 2020–February 2021. Follow up was done for at least 12 months and up to 18 months after enrolment for all participants, completing on the 28 February 2022.

For the primary outcome of adherence, we excluded a further 73 (2.7%) participants as they did not have adherence data, leaving 2584 (38% females; median age 36 years) for analysis (Fig. 1, Table 1). For the end of treatment outcome, 2538 participants (95.5%) were included (119 were not assessable: 2 missing treatment outcome and 117 transferred out), and for the unfavourable outcome at 18 months, before imputation, 2070 participants (77.9%) had their outcome known and 587 were not assessable (115 transferred out, 33 died and 438 lost to follow-up from the end of treatment). The

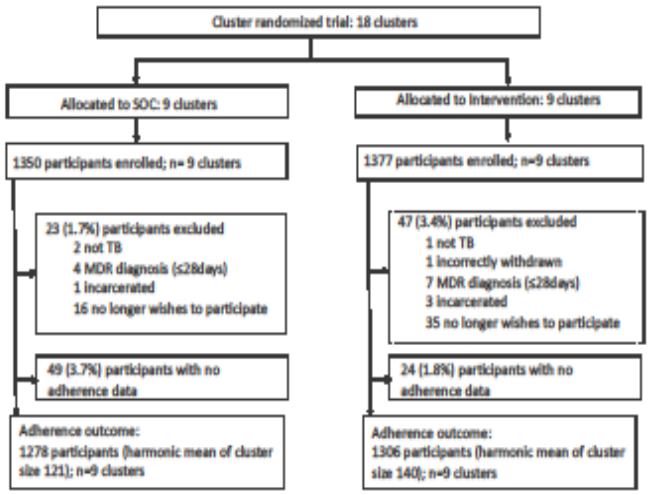

Fig. 1: Consort diagram for adherence population. n = number; MDR = multi-drug resistance; TB = tuberculosis; d = days.

Variable	Intervention		SoC		Total	
Number of clusters	9		9		18	
Type of clinic						
Primary health clinic	4		4		8	
Community health centre	5		5		10	
Number of participants	1306		1278		2584	
Province						
Gauteng	460	35.2%	316	24.7%	776	30.0%
Kwa-Zulu Natal	378	28.9%	469	36.7%	847	32.8%
Western Cape	468	35.8%	493	38.6%	961	37.2%
Age, median (IQR)						
Years	36	(27–45)	35	(27–45)	36	(27–45)
Age[a]						
<18 years	107	8.2%	65	5.1%	172	6.7%
Sex						
Female	481	36.8%	502	39.3%	983	38.0%
TB diagnosis						
Bacteriologically positive	1035	79.4%	893	70%	1928	74.4%
Country of origin						
South African	1273	97%	1217	95.3%	2559	
Ethnic group						
Black African	1165	89.2%	1218	95.3%	2383	92.2%
Education						
≤Grade 7	264	20.2%	270	21.1%	534	20.7%
Grade 8–11	557	42.6%	545	42.6%	1102	42.6%
≥Grade 12	485	37.1%	463	36.2%	948	36.7%
Marital status						
Single	924	70.8%	977	76.4%	1901	73.6%
Married/cohabitating	320	24.5%	241	18.9%	561	21.7%
Separated/divorced	30	2.3%	36	2.8%	66	2.6%
Widowed	32	2.5%	24	1.9%	56	2.2%
Hospitalised						
Yes	109	8.3%	118	9.2%	227	8.8%
Previous TB						
Yes	315	24.1%	297	23.2%	612	23.7%
Ever smoked						
Yes	416	31.9%	421	32.9%	837	32.4%
Alcohol consumption						
Never	788	60.4%	818	64.0%	1606	62.2%
Monthly or less	221	16.9%	177	13.8%	398	15.4%
Between 2 and 4 times/month	145	11.1%	188	14.7%	333	12.9%
Between 2 and 3 times/week	58	4.4%	56	4.4%	114	4.4%
≥4 times/week	93	7.1%	39	3.1%	132	5.1%
Missing	1				1	
Recreational drug use						
Yes	99	7.6%	79	6.2%	178	6.9%
HIV status[b]						
HIV positive -no ART	257	19.8%	264	20.7%	521	20.3%
HIV positive -on ART	320	24.7%	512	40.2%	832	32.4%
HIV negative	719	55.5%	497	39.0%	1216	47.3%
Missing	10		5		15	

SoC = Standard of Care; IQR = interquartile range; HIV = human immunodeficiency virus; ART = antiretroviral treatment. [a]70/107 and 36/65 were aged < 13 years in the intervention and SOC arms, respectively. [b]One cluster in the standard of care arm with different population and lower HIV prevalence resulted in imbalance by study arm for HIV status.

Table 1: Baseline characteristics of population included for adherence outcome (n = 2584).

CONSORT diagram and baseline characteristics for cohorts for the two secondary outcomes of end of treatment and unfavourable outcome at 18 months is available in the Supplementary Appendix (Supplementary Figs. S1 and S2 and Table S1).

For the primary outcome analysis population, most of our participants were adults (93.3%; 2412), Black African (92.2%; 2383) and single marital status (73.6%, 1901) and bacteriologically positive either on MGIT culture, smear or Xpert (74.7%; 1928). Over half (52.7%, 1353/2569) of participants were HIV-positive as tested by routine services, of whom, 832 (61.5%) were on ART. Baseline variables were in the most part similar by study arm, except for a higher proportion with bacteriological diagnosed TB and HIV negative in the intervention versus SoC and lower proportion of HIV positive on anti-retroviral therapy (ART) and those of African descent, in the intervention versus SoC arm (Table 1).

The proportion of participants with ≥80% adherence was higher 1056/1306 (80.9%, GM 81.0%) in the intervention arm compared to 650/1278 (51.6%; GM 50.8%) in the SoC [Adjusted risk ratio of 1.51 (95% CI 1.36–1.66) (Table 2, Supplementary Fig. S3). For the continuous adherence measure, the overall mean proportion adherence was higher 88.5% in intervention clusters compared to 69.7% in SoC clusters, giving a risk difference of 16.8 (95% CI 13.3–20.4) (Table 2, Supplementary Fig. S3). Looking at proportion of adherence months, the overall mean proportion with <80% adherence was 17.5% in intervention clusters compared to 43.0% in SoC clusters giving a risk difference of 25.4 (95% CI 19.5–31.3). Subgroup analyses for the primary adherence outcome showed improvement in adherence in all subgroups in the intervention arm (Fig. 2). The coefficient of variation for the primary outcome was 0.21.

The proportion with poor end of treatment outcomes was similar across the arms with 176/1279 (13.7%; GM 11.0%) in the intervention versus 172/1259 (13.7%; GM13.4%) in SoC arm, adjusted risk ratio 0.82 (95% CI 0.56–1.22) and adjusted risk difference −0.4% (95% CI -6.0% to +5.0). In the complete case analysis, for the composite unfavourable outcome at 18 months, proportions were lower in 216/1096 (17.1%) in intervention arm compared to 216/974 (22.3%) in the SoC arm however the effect was not significant with an adjusted risk ratio of 0.78 (0.53–1.16) (Table 2, Supplementary Fig. S3). Following multiple imputation for missing outcomes, the adjusted risk ratio was 0.83 (0.56–1.22).

Reasons for the poor end of treatment outcomes and composite unfavourable outcomes at 18 months are shown in Table 3. Approximately 20% of unfavourable outcomes were after the end of treatment. The most common outcomes were on treatment loss to follow up (n = 149) and deaths (n = 129) which make up 64% of all unfavourable outcomes. The proportions of, and reasons for poor end of treatment outcome per facility are shown in the Supplement (Supplementary Fig. S4a and b). Some clinics had high levels of on-treatment loss to follow-up which contributed to high proportion of poor outcomes during treatment and after end of treatment. A post-hoc sub-group analysis showed the intervention reduced the unfavourable outcome at 18 months among women and in the Western Cape cohort (Supplementary Fig. S5).

The sensitivity analysis that defined those who were on treatment for >10 months (280 days) as having an unfavourable outcome, showed that the proportions with poor end of treatment outcomes seemed to be higher in the SoC arm 202/1259 (13.7%; GM 15.6%) versus 197/1279 (15.4%; GM 11.9%) in intervention arm but there was no significant difference, with an adjusted risk ratio of 0.79 (0.54–1.18). The composite

	SoC n/N (GM%)	Intervention n/N (GM%)	Risk ratio (95% CI)[a]	P value
Primary outcome: adherence ≥80%[b]	650/1278 (50.8%)	1056/1306 (81.0%)	1.59 (1.36–1.66)	<0.001
Secondary outcomes:				
	SoC mean %	Intervention mean %	Mean difference (95% CI)[c]	P value
Overall % adherence	69.7%	88.5%	16.8% (13.3–20.4%)	<0.001
Secondary: percentage of months with <80% adherence	43.0%	17.5%	25.4% (19.5–31.3%)	<0.001
	SoC n/N (GM%)	Intervention n/N (GM%)	Risk Ratio (95% CI)[a]	P value
Poor end of treatment outcome[c]	172/1259 (13.4%)	176/1279 (11.0%)	0.82 (0.56–1.22)	0.31
Unfavourable outcome by 18 months[d]—complete case	216/974 (22.3%)	216/1096 (17.1%)	0.78 (0.53–1.16)	0.21
Unfavourable outcome by 18 months[d]—MI	241/1261[e] (19.1%)	234/1281[e] (15.5%)	0.83 (0.56–1.22)	0.32

SoC = Standard of Care; GM = geometric mean of percentage with outcome at the cluster-level; CI = confidence interval; MI = multiple imputation. [a]Adjusted for age group, sex, TB diagnosis, ethnic group, marital status, HIV/ART status and province, comparing intervention versus control. [b]Risk difference 26.1 (95% CI: 20.1%–32.1%). [c]Treatment failure, death, lost to follow-up or switched to an MDR regimen. [d]Composite outcomes of poor end of treatment outcome or recurrence/restarting TB treatment by 18 months. [e]Denominators excluded 66 and 43 participants who transferred out during treatment in the SoC and intervention arm, respectively. Numerator is the arithmetic mean of total number of unfavourable outcomes across the 25 imputations.

Table 2: Comparison of study endpoints of adherence, end of treatment and overall poor outcome in the SoC versus intervention arm.

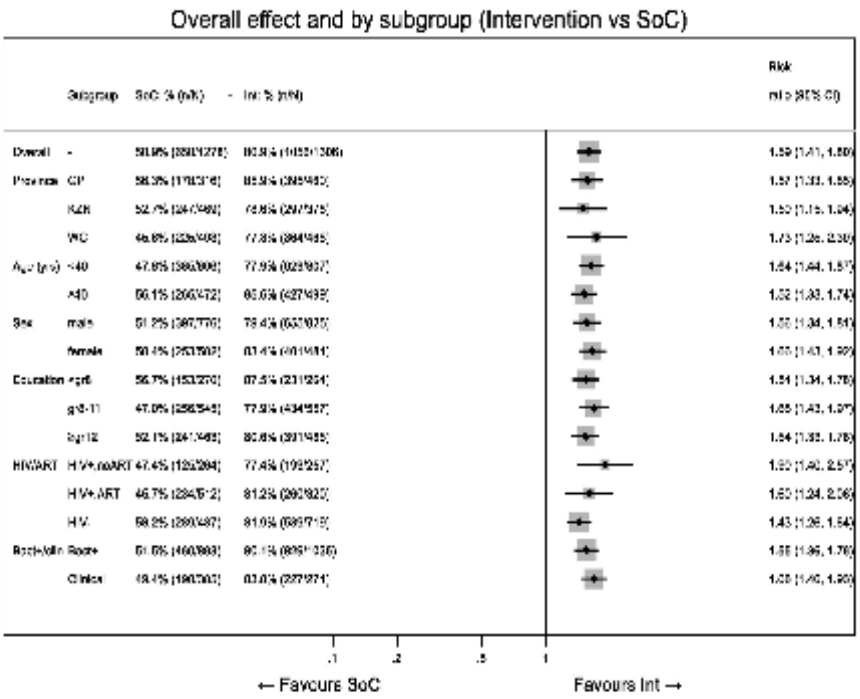

Fig. 2: Forest plot for subgroup analysis for primary adherence outcome (unadjusted). SoC = Standard of Care; Int = Intervention; CI = confidence interval; HIV = human immunodeficiency virus; gr = grade; ART = antiretroviral; Bact = bacteriological; CI = confidence interval; GP = Gauteng province; KZN = Kwazulu Natal province; WC = Western Cape province. The box represents the risk ratio; and the horizontal line through the box is the 95% confidence interval.

unfavourable outcome at 18 months, similarly it was higher in the SOC arm: 242/974 (24.8%; GM 24.8%) versus 234/1096 (21.6%; GM 18.1%) in intervention arm, but also with no effect, adjusted risk ratio of 0.76 (0.52–1.12) (Supplementary Table S2). Similarly, for the sensitivity analysis where those who had died between end of treatment and 18 months were defined as having an unfavourable outcome, the proportions with

	SoC	%*	%*	Intervention	%*	%*
Total unfavourable outcomes	216			216		
Poor end of Treatment outcome	172	79.6%		176	81.5%	
Treatment failure	30		13.9%	30		13.9%
Lost to follow up	81		37.5%	68		31.5%
Died	57		26.4%	72		33.3%
MDR diagnosis	4		2.3%	6		2.8%
After end of treatment	44	20.3%		40	18.5%	
MDR TB diagnosis	2		0.5%	2		0.9%
Culture positive	22		10.9%	23		10.6%
Restarted treatment	17		7.9%	12		5.6%
Positive TB sputum identified	3		1.4%	3		1.4%

SoC = Standard of Care; MDR = multi-drug resistant TB; TB = tuberculosis. *Percentage among those with unfavourable outcome.

Table 3: Components of the composite unfavourable outcome (poor end of treatment and after end of treatment outcomes) by arm.

unfavourable outcome as 234/992 (23.6%; GM 23.6%) in SoC and 231/1111 (20.8%; GM 18.2%) in the intervention arm, with an adjusted risk ratio of 0.79 (0.55–1.14) (Supplementary Table S2). Correlation between adherence and unfavourable outcome was examined as in Supplementary Table S4. There does appear to be a relationship as those with lower adherence show a higher proportion with poor outcomes. We show some measures of fidelity with regards to phone calls in Supplementary Table S6, that show a high proportion (78–81%) of episodes where a phone call was required, were successfully contacted.

Discussion

Among people treated for DS-TB, use of DAT with differentiated care resulted in improved treatment adherence when using a proxy measure of "days the medication monitor was opened" in the intervention versus SoC arm, when measured as either the proportion of participants with poor adherence (<80% versus ≥80%), or the secondary outcomes of overall adherence and percentage months with <80% adherence. Although adherence was improved, there was no significant difference in end of treatment outcome or unfavourable outcome at 18 months among people treated for DS-TB in the intervention versus SoC arms. There was some inbalance regarding HIV status and ART by arm which could have accounted for better adherence (lower numbers with HIV) and poorer treatment outcomes (lower % with HIV on antiretrovirals) in the intervention arm, although adjustment for HIV/ART status was conducted. These results are very consistent to the cluster-randomised trial done in China[10] where adherence was improved but did not lead to improved treatment outcomes or reduced recurrence, but differ from an individually randomised trial in Tibet, which used a treatment supporter and digital device (pillbox and video supported therapy for those with adherence challenges), and showed both improved adherence and treatment outcomes.[11] In addition, pragmatic cluster randomised trials conducted in four countries under the same protocol showed no improved treatment outcomes using digital adherence tools.[10]

While these results may seem counterintuitive, there are studies in other fields which show improved adherence yet fail to show a difference in biological outcomes.[21,22] The delinking of adherence and outcome is likely due to either the inaccuracy of the adherence measurement or the insensitivity of the TB treatment outcome measures. As found in the qualitative work where people reported opening the box to deal with the nuisance of reminders, it may be that in the SoC arm, box openings may have been less frequent since there were no reminders and no consequence to not opening the box in this group.[23] The problem is that there is no gold standard for measuring TB adherence. Evidence from HIV studies can be considered to understand how measurements using box openings may be a good measure of adherence as viral load suppression is a much more reliable indicator of adherence to treatment. A recent Cochrane review,[23] that compared electronic medication monitoring against viral load suppression in people living with HIV, found only 3 studies, with a total of 186 participants. Sensitivity of the adherence measured through box openings ranged from 60% to 88% and specificity ranged from 27% to 67%. In a recent study of 198 people living with HIV with MDR-TB, modeling identified a significant ($P < 0.001$), linear association between ART adherence and emergent HIV resistance, suggesting a strong association without a specific threshold.[24] Further studies to understand the relationship between medication openings and adherence through testing of metabolites may assist in understanding the data.

TB treatment outcomes can be insensitive[25,26] and may overestimate treatment success in a routine programmes, especially in the new TB era of molecular diagnostics (and a higher proportion of smear negative TB on treatment), where treatment success is mostly made of treatment completion rather than cure. Clinical trials use more robust outcomes[27] that include multiple cultures and post treatment followup and that may be why there was a more a more direct association between adherence and treatment outcomes identified in TB treatment trials. In our pragmatic study, we collected one sputum culture at month 6 and another at month 18 which may not have been sufficient to detect progression to treatment failure or relapse. In addition, due to operational difficulties, COVID-19 disruptions and participants being unable to produce sputum, we were only able to determine bacteriological outcomes in 30.8% at 6 months and 29.1% at 18 months, speaking to the difficulties with outcomes definitions. A study conducted among people with DR-TB showed that bedaquilline adherence through 6 months independently predicted end of MDR-TB treatment outcome,[12] and it may be that more intensive bacteriological monitoring in routine DR-TB programmes may have had a different result.

As with HIV,[28] successful TB treatment outcomes may not require perfect treatment adherence for successful treatment outcomes, i.e., the treatment regimen may be more "forgiving" than originally assumed or the timing of non-adherence may play a role. Since the end of the DOTs era, there has been little data exploring TB treatment adherence, and potentially the lower adherence seen in our SoC arm may be sufficient for a TB cure. Historically there were regimens, particularly in the continuation phase, that were thrice weekly or at least not daily (5 days per week),[29] therefore the lack of improvement may reflect the forgiving nature of the regimen for most patients. The analyses of the adherence data of the treatment-shortening trials, as well as the correlation of adherence and outcomes, may

however contradict this.[5] Further analysis to understand whether patterns of adherence and timing of poor adherence are related to outcomes are planned.

We have considered whether the discordance between our adherence and treatment outcomes, could be that the study population (and therefore the control) may have been less "hard-to-treat" (as described by Imperial et al.) which refers to PWTB with smear positivity and cavitatory lung disease, who do not respond well to treatment.[5] As our study had very few exclusion criteria and included all people with drug susceptible PWTB in outpatient clinics, we think this is unlikely. Compared to trial participants, we did have a lower proportion with smear positive disease (70% versus 90%) and although we didn't have chest x-ray findings, we had a higher proportion of participants who were HIV positive in our study population (53% versus 16%), indicating that we may have had less cavitatory disease.

When considering whether this intervention should be implemented, consideration of issues of feasibility and acceptability are important. The published work from this study on qualitative measures such as feasibility and acceptability have shown that the medication monitors are very well received by people with TB and health care providers[29,30] and that may indicate that since there was no harm caused by the intervention, it may still be worth considering. Further supporting evidence for acceptability have also been published from studies including Ethiopia, Tanzania, and Philippines.[31]

A major strength of our study was that it was a large-scale implementation trial and one of the first trials in the world to measure TB adherence and TB treatment outcomes among patients treated for DS-TB using real-time adherence monitoring. Strengths include: equal representation of sexes; cluster randomised design that allowed comparison in a more routine setting; the documentation of adherence using the silent monitors in our control sites and the follow up of patients after treatment completion. The study involved three regions of South Africa, with varied TB disease burden, health system infrastructure and socio-economic factors that influence behaviour, so demonstrating flexibility and adaptability and generalisability of the intervention. Our study was complemented with qualitative and economics research which allows a more holistic evaluation of DAT.[23] Our initial data indicate that the differentiated care intervention was implemented with high fidelity.

Weaknesses include the relatively small number of sites. We also relied on standard measurement of outcomes although we did attempt to include TB cultures, the sputums were often not collected at the six and eighteen month points, and loss to follow up of participants. Another weakness of the study was that our adherence data was not supported by the measurement of another objective adherence measure e.g., INH urine metabolites.[28] The pragmatic nature of the trial was a strength as it allowed for real-world implmentation but it also meant that problems such as COVID-19 clinic shut-downs and social unrest impacted our measurements of outcomes and increased loss to follow up, although this would have affected both arms. There were some facilities in high crime areas where clinic closures were common for safety reasons and which prevented home visits where these would have been required.

In conclusion, our trial supports further evaluation of digital adherence tools for adherence support for TB as we did demonstrate an improved adherence by using the medication monitor and differentiated care package in people with DS-TB in South Africa. Although there was an improved adherence, there was no significant difference in unfavourable outcomes in people with DS-TB. The reasons for the limited impact of improved adherence on clinical outcomes are likely complex, may be related to patterns of adherence and differential use of the medication monitor between the arms is possible. If the impact increased adherence on unfavourable outcomes in some sub-cohorts, for example among females is real, this is potentially a very important intervention. Also, there might be a need to further improve support by allowing for more patient-centred care with more involvement of patients/healthcare workers to co-develop interventions.

Contributors

KLF, SC, PN, CO, NM, KV and CMCM conceptualised the study and interpreted the study findings.

RM, NX, IM, PH, contributed to study implementation and collection of data.

KLF and IM verified the data.

KLF analysed the data.

SC an NM wrote the original draft and revised subsequent versions of the manuscript.

NM, CO, IJ, PN, KV, KLF, SC, IR, DC, RM, LM, PH, NX and CMCM reviewed and edited previous versions.

All the authors read and approved the final manuscript.

Data sharing statement

Study protocol, Statistical analysis plan and data will be available upon submission of a request to the Aurum Data Governance committee.

Declaration of interests

CO received honoraria from MSD in Dec 2022 and November 2023 for consultation at their Africa ART meetings. PN has received support from BMGF to attend the Union Conference on lung Health and SA TB Conference. All other authors declare that they have no competing interests.

Acknowledgements

The study is funded by (1) Bill & Melinda Gates Foundation (OPP1205388), (2) TB REACH Wave 6 project of Stop TB Partnership (STBP/TBREACH/GSA/W6-34), and (3) South African Medical Research Council through the Strategic Health Innovation Partnerships.

We would like to thank the following: Ekurhuleni, City of Cape Town, eThekwini.

Districts and the Ekurhuleni Health District Research Committee (EHDRC) for allowing us to conduct the study in their districts. The study coordinators and their field-based teams of research assistants and interns for their assistance with data collection.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102745.

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Appendix B – Ethical clearance certificates

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

15 November 2018

EMAILED & COURIERED

Ms R Wills

Regulatory Manager
The Aurum Institute: The Ridge
29 Queens Road
Parktown
2193

Fax: 086 759 2728

Dear Ms Wills,

PROTOCOL: AUR2-1-244 - TB MONITORING ADHERENCE AND TREATMENT ENDPOINTS PROJECT: THE USE OF MEDICATION MONITORS AND A DIFFERENTIATED CARE APPROACH TO IMPROVE TB ADHERENCE

ETHICS REFERENCE NO: 180705

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial has been approved by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol/Expert Reviewer. Date of Meeting where trial was reviewed: 27 July 2018.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. It is the responsibility of the Sponsor and Principal Investigator to ensure, where required, that relevant approvals are in place and compliance with the following is adhered to before a trial may begin:

- If trial is being conducted in Provincial Health facilities: Approval from the Hospital CEO / Clinic Manager / District Research Committee (whichever is applicable) be obtained.
- The study is submitted onto The National Health Research Database (NHRD).
- The relevant approvals are uploaded onto the NHRD system: Ethics Approval, SAHPRA Approval, Hospital CEO / Clinic Manager / District Research Committee Approval.

* A copy of the SAHPRA Approval and/or SAHPRA Notification letter must be submitted to the Ethics Secretariat Office for record purposes (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE).

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study.

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:
* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:
* The University of the Witwatersrand, Human Research Ethics Committee requests that the SAHPRA Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:
* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the South African Health Products Regulatory Authority and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:
* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING:
* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE:
* The South African Department of Health, South African Health Products Regulatory Authority requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator(s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

8.2 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

9. **WE AWAIT YOUR RESPONSES AS REQUESTED:** Ensure to have these documents forwarded at the earliest for the HREC records.

* SAHPRA Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).

* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,

PROF CLEMENT PENNY

For and on behalf of the Human Research Ethics Committee: (Medical)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 September 2018

HREC REF: 452/2018

A/Prof C Orrell
Desmond tutu HIV Foundation
N1.21.15 WBN
FHS

Dear A/Prof Orrell

PROJECT TITLE: TB INNOVATIONS ADHERENCE PROJECT: THE USE OF MEDICATION MONITORS AND A DIFFERENTIATED CARE APPROACH TO IMPROVE TB ADHERENCE

Thank you for your response letter dated 27 August 2018, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, including the following documentation:

1. PI Synopsis v1 dated 29 June 2018
2. TB Monitoring Adherence and Treatment Endpoints PROTOCOL v2.0_28August2018-CAPE-TOWN
3. Appendix 1_Interview Guide-Participants _V1
4. Appendix2_Interview Guide-DoH Key Stakeholders Facility Staff_V1
5. PIS_ICF_Main_study_ADULTS_intervention_v2.0_28Aug2018-CAPE-TOWN
6. PIS_ICF_Main_study_PARENT_intervention_v2.0_28Aug2018-CAPE-TOWN
7. PIS_ICF_Main_study_ASSENT_intervention_v2.0_28Aug2018-CAPE-TOWN
8. PIS_ICF_Main_study_ADULTS_control_v2.0_28Aug2018-CAPE-TOWN
9. PIS_ICF_Main_study_PARENT_control_v2.0_28Aug2018-CAPE-TOWN
10. PIS_ICF_Main_study_ASSENT_control_v2.0_28Aug2018-CAPE-TOWN
11. Patients_qualitative _PIS_ICF_v2_28August2018-CAPE-TOWN
12. Stakeholder_qualitative_PIS_ICF_V2_28August2018-CAPE-TOWN
13. Summary budget

Approval is granted for one year until the 30 September 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix C – Report from “Turnitin” Plagiarism software

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