

**STRUCTURE AND AGENCY
IN THE ECONOMICS OF PUBLIC POLICY
FOR TB CONTROL**

NICOLA FOSTER

Thesis presented for the degree of
Doctor of Philosophy
in the
Health Economics Unit
School of Public Health and Family Medicine
University of Cape Town

FEBRUARY 2019

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NICOLA FOSTER

BPharm, MPH (Health Economics)

Thesis presented for the degree of
Doctor of Philosophy
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This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. The contribution of the candidate to the papers is further delineated in the publications section of Chapter 1.

NICOLA FOSTER

FEBRUARY 2019

Abstract

Globally, Tuberculosis remains a devastating disease, despite the availability of treatment. The disease is associated with poverty, and those with the disease incur a high cost of accessing care, while simultaneously experiencing income loss due to a loss in productivity. A key challenge in TB programmes remains the accurate diagnosis of the disease, especially in people who are HIV positive. Diagnosing TB can be very resource intensive and the accuracy of diagnosis is dependent on a range of disease, health service organisation and provider behaviour factors. This thesis seeks to enhance understanding of how the behaviour of healthcare workers mediates the value of TB diagnostic algorithms, and how this may affect the costs, outcomes as well as the economic burden associated with the disease in South Africa. The work presented is based on empirical work done alongside a pragmatic cluster randomized control trial. Empirically, it examines the longitudinal economic burden of TB diagnosis and treatment in South Africa. The discrepancies between the time at which patients incur the greatest cost and income loss, and the available social protection are highlighted. Based on empirical work, a purpose-built state-transition mathematical model of TB diagnosis and treatment was developed to estimate the cost-effectiveness, from the perspective of the health service and the patient, of health systems interventions to strengthen TB diagnosis. Recognising healthcare workers as those who ultimately express policies, the behaviour of healthcare workers was included in the cost-effectiveness analysis by 1) using data from a pragmatic trial reflecting routine practice and clinical decision-making at the time of the study; 2) developing a conceptual framework of the relationship between behaviour at decision points and disease outcomes; and 3) investigating how these interactions may influence the value of the diagnostic algorithm. Possible public policy levers to improve TB diagnosis in healthcare facilities, as well as the potential mediators of costs and effects were explored. The thesis concludes with recommendations for further methodological work to expand on the approach explored in this thesis to improve how heterogeneity in estimates of cost-effectiveness is presented to decision-makers.

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“We make no apologies for making these excursions into other fields, because the separation of fields, as we have emphasized, is merely a human convenience, and an unnatural thing. Nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields.”

Richard Feynman (1918 – 1988)

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Preface

In 2006, as a newly graduated pharmacist, I was required to work in a public health facility in South Africa for one year before being allowed to register as a qualified pharmacist. The clinic that I was assigned to, was situated within a farming community in the Western Cape of South Africa. On my first day, I was given the keys to ‘my’ dispensary, opened the door and was met by a staggering pile of brown patient folders, all with prescriptions waiting to be dispensed. While I had arrived at 8am, patients had arrived well before 6am to claim a place in the queue for when the clinic doors opened at 7am. Upon opening the pharmacy hatch, a sea of faces was looking back me, impatiently awaiting their medicine as a last step in a long process, hurriedly on their way to work. I was rapidly initiated into the process, the never-ending paracetamol prescriptions for pain-related conditions that required a much more holistic approach; the delays between ordering medicine and its eventual arrival at the clinic; the need to split packets of medicine between patients to make the available stock stretch in the face of impending stockouts, triggering earlier repeat visits for patients. But what I also developed great admiration for, was the resourcefulness and resilience of staff at public health facilities, where a plan could be made around a lack of key resources, and where nurses would stop by the pharmacy to lend a helping hand at the end of their day. I observed how staff would reorganise the way the clinic provides services, to reduce waiting times, consolidate staff workload and improve patient satisfaction, where possible. It was a world, far removed from the spaces where neat, tidy and linear policies were drafted.

By the end of that year, I had learnt a great deal about the complexities of health service provision, the resilience of staff and how inexorably the clinic functions as part of the community. Some of my experiences during that year, led to a series of research questions on possible models for providing pharmaceutical care. Given my work as a pharmacist in the district, I was invited to share my research findings at meetings with district management and with the pharmacists and nurses working in the district. These meetings allowed a bidirectional dialogue, with me presenting the experiences of patients. This was followed by collective discussions on how to reorganise services to improve patient outcomes in a manner that would be sustainable in each of the clinics, given constrained resources. Those experiences taught me the importance of the daily discretionary

decisions made by healthcare workers. More broadly, it highlighted decision-making at the district level, where managers must decide on how services are organised with what is available, while attempting to comply with a myriad performance measures set by provincial and national government often at the whim of a global community.

The dynamics of the decisions faced by these frontline decision-makers, and how the actions taken as a result of these decisions influence population-level outcomes (including the financial burden on the patient) are often discounted. However, it is these decisions, at the very heartbeat of the health system, that ultimately amends the effectiveness of policies (both positively and negatively) and an understanding of this complexity is crucial to decision-making in decentralised health systems. It was only later, that I discovered the works of the political theorist, Lipsky who wrote about street-level bureaucrats and how the values and practices of those who implement policies, fundamentally change the direction and vision of the policy. Similarly, Ostrom introduced the idea of public entrepreneurship to describe how individuals (or groups) organise public institutions to provide goods and services. She noted that the capacity in a system to engage in public entrepreneurship is political, and that the ability to do so is enabled and constrained by a set of formal and informal rules. The drivers of behaviour and motivation of public entrepreneurs are complex, as they have access to more resources than entrepreneurs in the private sector but are also more constrained by bureaucratic institutional structures. My understanding of the relationship between the actions of actors and how they are dictated by institutional structures was enriched by the work of the social theorist, Coleman who studied the intersection between micro - and macro-level interactions. The work of these scholars would give language to, and deeper understanding of my experiences working in the public sector and would go on to shape the work that culminated in this thesis.

CHAPTER 1: INTRODUCTION

1.1 Introduction

Globally, Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) remain leading causes of premature mortality in high-burden countries, including South Africa. TB has been found to be associated with poverty, malnutrition and cigarette smoking (1–4). In an analysis of longitudinal household survey data in South Africa, Ataguba et al (2011) found that the poorest 40% of the population accounted for 65% of the TB disease burden (5). It has been observed that TB epidemics worsen in societies with failing public service capacity (6); and that identifying people with active TB and initiating treatment as early as possible is crucial to reducing transmission and achieving TB control. Within a global priority setting framework of working towards Universal Health Coverage (UHC), and given the unlimited need for healthcare, to be met with limited resources, there is an ever-increasing emphasis on comparing the value of investments in health care, to optimise the use of scarce resources and to strategically plan resource allocation (7).

Historically, decision-making for public policy has often focused on technical solutions, such as drugs and diagnostics, and this has also been a feature of the global TB control agenda (8–10). However, there is a growing recognition that solely technical solutions do not produce the population-level effectiveness initially predicted (11–14). The implementation of XPert MTB/RIF, a novel TB diagnostic was an example of this gap between expected and observed population-level effectiveness (15). The test was initially lauded for its improved ability (compared to smear microscopy) to detect TB especially in HIV positive patients, which was thought to potentially reduce TB-associated mortality. It is hypothesised that the reasons for the differences between the outcomes of single technical interventions and the implemented public policy, can be ascribed to the way in which these interventions are communicated to those who interact with the beneficiaries as well as how they interact with other investments (13,16–19). When conducting cost-effectiveness analyses alongside clinical trials that are evaluating the potential cost and impact of technical solution, behaviour and resource constraints in the

context are controlled to various degrees depending on the study design (16). To provide a more accurate understanding of what the population-level effectiveness and resource use may be, there is a need to understand 1) how resources will be made available to support the intervention and 2) how health care workers as agents in the health system may respond to the introduction of the intervention to ensure that resource allocation is optimised.

Economic evaluation represents a set of analytic approaches to evaluate the value of public policy investments, whereby the incremental costs and outcomes of investment options are compared (20). These analytical approaches typically fit into a broader explicit or implicit decision-making process, either at a global, a country – or at a local level. Ideally these processes would also be iterative, re-evaluating whether the implementation of certain technologies remain cost-effective unless compared against a newer (more expensive) test (21). Economic evaluation is intended to provide guidance for making decisions to maximise outcomes within a finite set of resources, typically the budget of a programme (22). It has been argued that under the conditions of a perfectly competitive market, in the long run, the only resource constraint of interest would be the budget constraint (21: 20). However, this theory assumes that all other constraints to achieving a specified outcome, including skilled human resources, technology, or infrastructure, could ultimately be relaxed by purchasing the additional resources needed (24,25). However, within an imperfect market system, this is unlikely to hold true and it would be more difficult to alleviate some constraints by purchasing additional resources than others (26). This is because the outcome (as well as the costs) of the implementation of a policy is partly mediated by the ways in which policies are interpreted and reconfigured by those who implement them (27).

Heterogeneity in the implementation of investments as a function of constraints in the health system, might be explicitly explored by differentiating between proximal and distal constraints; with distal constraints referring to constraints that mediate an interaction with a direct impact (28,29). For example, while it would be possible, with an increased budget, to employ additional healthcare workers to implement an intervention of interest (proximal constraint), there may be a limited number of trained healthcare workers in the country and additional investment in education and training is needed (distal constraint). Without the additional investment in education, it is possible that the

desired outcome may not be fully achieved, resulting in a sub-optimal allocation of resources (13). While some economic evaluations will have an expanded scope by including the costs associated with purchasing the additional support required, by for example, including the costs of the development of the guideline, unless the causal pathway between the distal constraint and the outcome of interest is well understood, it is unclear what the resultant impact on the efficiency of the investment may be (30,31). In the remainder of the thesis, economic evaluations with an expanded scope (that include the costs or outcomes of additional support), will be referred to as economic evaluations of health systems investments. This is to distinguish these investments from a broader category of work considering investments in public health where the investment is made outside of the health system with the impact on a range of development indicators evaluated (32).

In addition to the challenge of estimating the mediating effect that constraints may have on the costs and outcomes of interventions, other challenges related to evaluating health systems investments include;

- how to evaluate the costs and outcomes that fall on other public sectors, the spill over costs and outcomes;
- the way in which the characteristics of social systems, for example the adaptation of guidelines and changes in behaviour are dealt with analytically (33–37); and
- how the timing of outcomes is included.

The case of the dynamic nature of social systems, can be explained by considering the interaction between disease transmission and health care worker behaviour. In the evaluation of public policies related to transmittable diseases - including the costs and outcomes related to transmission of the disease and how this in turn influences the burden of need in the population - will affect the cost-effectiveness of interventions (38,39). For example, where disease elimination is being modelled, it has been shown that the cost-effectiveness of a specified intervention will decline as elimination is approached, with the cost per additional case identified increasing (40). However, in any system these changes are likely to coincide with a corresponding change in the behaviour of healthcare workers in response to the decline of the prevalence of the disease and as other competing

interventions are implemented. The introduction of new interventions in the system may therefore result in a non-linear increase of the effectiveness (and costs) of interventions over time (17).

Similarly, the quantification of spill over costs and outcomes may pose a challenge when evaluating certain investments. Investment in healthcare will either increase or reduce the productivity loss associated with ill health, as well as the costs incurred by patients and their families (3,41,42). This effect will also differ between the poor and the wealthy in the community, and this distribution of effect between poor and rich may be of interest to policy makers when deciding between alternative investment strategies. However, these costs and effects will fall outside of the health sector, on the social welfare system or in countries with an insufficient state social safety net, these costs will fall on families and communities.

In evaluating health systems investments, the challenge therefore is to identify the scope of the analyses and how (and whether) the different characteristics of a system will or can be included in the analyses. Previous studies that expanded on the traditional cost-effectiveness framework to include system constraints, focussed on constraints that are amenable to monetary investments, specifically those related to the number of healthcare workers, their training, health service infrastructure and technology (43–45); or considered how institutions are restructured due to investments (46). However, there remains a paucity of work explicitly considering how the interaction between the structure of the system, the disease characteristics and the behaviour of healthcare workers may influence the estimation of costs, outcomes and the allocative efficiency of alternative policy options once implemented. Work presented in this thesis addresses some of this gap in the literature, using the example of an evaluation of a new diagnostic test used in TB case finding in South Africa.

1.2 Aims and Objectives

Given the areas of debate outlined above, the aim of the thesis is to explore how the behaviour of healthcare workers alters the value of clinical guidelines (specifically TB

diagnostic algorithms), and how these changes may affect firstly the value of the implemented diagnostic, and secondly the economic burden of a disease on patients, their households and their social networks.

The objectives of the work presented in the thesis therefore are to:

1. Develop a conceptual framework describing the TB diagnostic related interactions between healthcare workers and the system within which they work;
2. Estimate the economic burden of TB diagnosis and treatment in South Africa;
3. Develop a mathematical model representing the TB diagnostic pathway in South Africa, with an emphasis on the decision points of healthcare workers;
4. Determine the cost-effectiveness and cost-utility (from a societal perspective) of investments to support the implementation of new TB diagnostics in South Africa;
5. Propose and reflect on approaches for modelling how healthcare workers' behaviour - in response to the resources available to them - will alter the value of the implementation of new TB diagnostic technologies.

In this thesis, I will propose a set of considerations for how an economic evaluation framework may be expanded to include interactions related to the decision-making of healthcare workers in response to constraints experienced within their environment. In addition, I will explore how implementation may vary as a result of differences in behaviour, and this in turn may change our predictions for resource allocation. To do this, the analysis draws on theory related to the behaviour of agents in systems as well as decision-making under uncertainty. The example of the implementation of a new TB diagnostic in South Africa is used to explore possible approaches and to present the arguments.

1.3 Publications

The above objectives are addressed in two manuscripts and a supplementary appendix, of which one paper is published, and one paper plus the supplementary appendix has been drafted and received feedback from co-authors. *"I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the*

following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s)”

Since the work has been done as part of a large multi-disciplinary team, my contributions to each of the papers are outlined below:

Chapter 5:

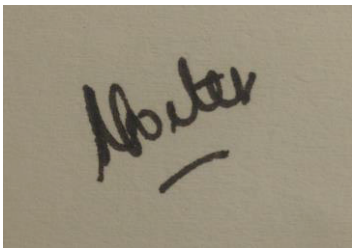
Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G and Sinanovic E. 2015. The economic burden of TB diagnosis and treatment in South Africa. *Social science and medicine*, 130: 42 – 50.

As the first author, I contributed to the design of the patient cost study and the data collection tools, as well as the integration of the patient cost questions within the trial survey platforms. I worked under the guidance of the study principal investigator, Anna Vassall, who provided extensive feedback and comments on the work. I was responsible for training interviewers on how to ask the patient costs questions, piloting and refining the questionnaire further, as well as following up on issues of data quality or where there were queries. Kerrigan McCarthy was the project manager for the trial and therefore led the implementation of the epidemiological study. For the second cohort, the treatment cohort, where we were sampling from the same facilities, Lebogang Ramma and Lucy Cunnama managed follow-up interactions with study staff. In addition, I liaised with the Aurum data management team for frequent reviews of the economics data and wrote STATA code to check data quality, followed by the code and analysis of the longitudinal dataset, I also presented interim findings to the funders and at conferences, wrote the first draft of the manuscript and revised based on co-author feedback.

Chapter 6:

Foster N, Cleary S, Cunnama L, McCarthy K, Ramma L, Siapka M, Sinanovic E, Churchyard G, Fielding K, Grant AD and Vassall A. Strengthening health systems to improve the value of Tuberculosis diagnostics in high-burden settings: a cost and cost-effectiveness analysis. *Drafted*.

This paper is part of work done within a large collaborative project. I led the development of the model as well as the analysis. I wrote the first draft of the paper and extensively revised based on feedback from co-authors. The epidemiological team (specifically Kerrigan McCarthy and Katherine Fielding), through the leading of the trial, collected the outcomes data and matched outcomes data from various sources to the primary dataset. This process is described in more detail in Chapter 4 of the thesis. Mariana Siapka created a merged dataset of the economic variables with the various trial datasets, the inclusion and exclusion rules used when combining the datasets were developed, discussed and approved between myself, Anna Vassall and Katherine Fielding. I developed the mathematical models that are presented in the thesis, with guidance from Susan Cleary, and Anna Vassall. I am very grateful to Alison Grant, Kerrigan McCarthy, and Katherine Fielding for providing advice on the epidemiological interactions.

A photograph of a handwritten signature in black ink on a light-colored, textured surface. The signature is written in a cursive, slightly slanted style and appears to read 'Nicola Foster'. There is a short horizontal line drawn below the signature.

NICOLA FOSTER
CLTNIC004
FEBRUARY 2019

1.4 Structure of the remaining chapters

The thesis is presented in eight chapters, with the current chapter introducing and outlining the body of work. The policy context and decision structures globally and in South Africa are introduced in Chapter 2, where there is a description of the history of TB control policies, how these intersected with major public policy changes and the presumed impact on the epidemic. Lastly, the present state of the epidemic, and potential implications for the need for public sector resources, is discussed.

In Chapter 3, theories related to our understanding of how the market for healthcare functions are outlined, followed by a review of theories that aids our understanding of behaviour and agency. Lastly, the chapter is concluded with a discussion on how these theories influence our understanding of approaches to evaluating health systems investments. Key methodological debates are identified. The chapter also includes an outline of the theoretical foundations of economic evaluation as an analytical approach. Issues discussed include the conceptualisation of costs, and outcomes, time preference, heterogeneity and the transferability of the results. The latter part of the chapter provides a theoretical framework for analysing the way in which the resource use and outcomes of decision-making, at various levels, are shaped by the way in which agents in the health system respond to how the structure of the health system is organised.

The methodological approaches used in the thesis are described in Chapter 4. The chapter initially outlines the approaches used, with further details of each of the specific analyses provided in the results chapters (Chapters 5 to 7). A detailed write-up of the development of the mathematical model as the primary analytical method used in the thesis is provided. Empirical literature is reviewed and presented, as pertaining to the interactions mathematically expressed.

In the results chapters (5 to 7), Chapter 5 presents a longitudinal patient cost study that was used to identify at which point in patient care associated with TB, the greatest economic burden of ill health is experienced. This section also introduces the concepts of an extended economic burden on not just individuals and their ability to pay for healthcare but also on households, and their social networks. This analysis also provides

the utilisation parameters that become the patient pathway through care upon which the model presented in Chapter 6 is based.

Chapter 6 presents a mathematical modelling approach to analysing the context within which interventions are placed, and how this may affect decision-making for investing in complementary investments to the TB diagnostic pathway. Data from a pragmatic cluster randomised control trial, and the longitudinal patient cost study presented in Chapter 5, were used to parameterise the resource use and treatment outcomes of individuals entering the model. Secondary data were used to parameterise the disease progression of individuals in various states in the model. Given the pragmatic nature of the trial, as well as the lack of a gold standard TB diagnostic test, data on true TB status were not collected. The model was calibrated to the trial data of time to mortality and time to treatment started.

Chapter 7 builds on this approach by exploring how the behaviour of healthcare workers may influence the value of the TB diagnostic algorithm. This model analysis represents a more nuanced prediction of the cost-effectiveness of the proposed investments. Implications for economic evaluation as a methodological approach are discussed.

Finally, Chapter 8 reviews and discusses the findings of earlier chapters and makes recommendations for a contextually nuanced decision-making process to inform decentralised decision-making structures embedded in the South African health system. It also presents an argument for how public policies may be designed differently if we considered the perspectives of those beyond the household (as a community) who provide financial support, caregiver time and other supportive resources.

The novel contributions of this thesis are outlined in terms of their empirical, analytical and conceptual contributions. These include the first study empirically showing how the costs to patients and their ‘community’ change as patients move through care from first symptoms to the end of treatment, in South Africa. In addition, it contributes to our understanding of the resource – and behavioural drivers associated with TB diagnosis. It includes detailed cost analyses of the cost of TB diagnosis and patient movement through care. The conceptual contribution of the thesis relates to the development of a framework for exploring how the interaction between resource availability and healthcare worker

behaviour in the health system may be incorporated into mathematical modelling for resource allocation. It does this by constructing healthcare worker utility functions from a combination of patient-level data and empirical literature. Lastly, the analytical contributions include the development and calibration of a mathematical model of patient movement through care.

CHAPTER 2: THE ECONOMIC HISTORY OF A CONSUMPTIVE DISEASE

2.1 Introduction

This chapter presents an overview of TB control policies globally and in South Africa, with an emphasis on how these policies evolved over time within a particular macro-economic environment. The development of global and local policies within the social context of the country is described. Understanding how history has shaped both the institutions, as well as the population and healthcare worker responses to TB control policies is useful in understanding how this history is still shaping the context of policy implementation today. Policy and guideline changes are influenced by current knowledge of the TB epidemic, but also by changes in the broader political climate and views on resource allocation. Tuberculosis is a good example of how epidemics are shaped by public policies, often implemented outside of the health system – most notably here housing, the mining sector and social welfare.

2.2 Public policy and TB control

The disease Tuberculosis (TB), is caused by a bacterium, *Mycobacterium Tuberculosis*. The disease is an ancient human zoonotic disease and known by many names, among others consumption, phthisis, scrofula (for extra-pulmonary TB), Pott's disease, and yaksma. Many of these names refer to the way in which the disease 'consumes' the patient, leading to the wasting away of the patient. More recently, it has been called the white plague. This was to contrast TB against another very deadly disease, the black plague, as well as to signal the characteristic pallor associated with those who suffer from the disease (46: 2). The disease is associated with conditions outside of the health system such as overcrowding, poor living- or working conditions, indoor smoking, poor nutrition, infection with HIV which suppresses the immune system, as well as exposure

to airborne irritants such as silica dust (48,49). TB is transmitted through airborne transmission (50), but it is thought that most transmitted infections lead to latent TB, that is only activated once the infected individual's immune system can no longer suppress the bacteria, with a resultant progression to active disease (51). It is only when the disease is active in the individual's body that it can be transmitted and leads to ill health and death.

Public policies to control epidemics are primarily aimed at firstly 'removing' the person who is infected from the population, to prevent the spread of the disease at a population level. Individuals are 'removed' from the population either through diagnosis and treatment initiation or through the physical separation from others who may become infected, through quarantine in sanatoria as an example (39). Alternatively, efforts are focused on preventing transmission by reducing individuals' probability of contracting the disease through preventative strategies such as vaccination. These interventions are prioritised under the hypothesis that, at a population level, reducing transmission will reduce mortality, long-term disability (morbidity) and the consequences of the medical poverty trap (worsening impoverishment) on households (52).

In the pre-antibiotic era, TB control policies were focused on segregating those with TB in sanatoria to prevent the transmission of the disease, and treatment included bed rest, a healthy diet and fresh air, in the hope that this would support the body to fight the infection (53). In 1882, Koch identified the organism *Mycobacterium tuberculosis* as the cause of TB, which launched a new era for TB control strategies. By 1920 the BCG vaccine was developed, which consisted of a weakened version of the bacteria to stimulate the immune system to contain the disease. In the 1930's, country-level TB control policies included the testing of cattle for TB, with zoonotic TB being considered a possible driver of the epidemic in humans. This, in conjunction with the increased use of pasteurised milk, is thought to have helped prevent animal to human transmission of bovine TB. In 1944, with the advent of antibiotics, and the discovery and development of firstly Streptomycin, followed by Isoniazid (1952) and Rifampicin (1968), the focus of TB control policies shifted away from preventative, psychosocial and community interventions to biomedical innovation with a specific focus on anti-microbial agents. By 1950, after the end of World War II, the prevalence of TB in developed countries (here using the example of the city of London) had dropped to below 0.1% from 0.5% in the

pre-antibiotic era (54). Improved living conditions, the control of bovine TB, improved nutrition as well as the availability of TB treatment are thought to have contributed to this shift. Housing reforms post World War II, particularly the 1919 UK housing act, is also thought to have contributed due to slum clearance and improved living standards, reducing household overcrowding and TB transmission (54).

In 1995, the World Health Organisation (WHO) declared TB a global health emergency, followed by the introduction of a comprehensive treatment strategy, called the Directly Observed Treatment Short Course (DOTS). The strategy was initially introduced based on epidemiological modelling of the epidemic and possible interventions suggesting that this combination of interventions would curb the epidemic (55). The focus of the DOTS strategy was to start treatment as soon as possible and improve patient adherence to the regimen to ensure that the course is completed, avoiding recurrence, transmission and the development of resistance.

The five components of the DOTS strategy were:

- government commitment,
- case detection by microscopy,
- standardised treatment,
- regular drug supply, and
- standardised recording and reporting (56,57).

The emphasis on government commitment and regular drug supply signalled an awareness of the importance of the health system as an organisation in delivering effective interventions. However, the broader policy conceptualisation and implementation was characterised by top-down policy processes, presenting to countries an ideal model to implement with limited country consultation of possible models for adaptation or specific constraints to implementation (58,59). TB control policies further evolved based on the country disease burden; in low-prevalence countries, policies shifted focus towards screening and treatment of TB in migrant communities.

In South Africa, the emergence of the HIV and AIDS epidemic led to a burgeoning in TB deaths, with TB becoming the most prevalent opportunistic infection in this

population and the primary cause of death in those HIV positive not on Anti-Retroviral Therapy (ART) (60,61). The social drivers of the dual epidemics are thought to be multifaceted (53). The HIV epidemic got a foothold into the South African population during Apartheid's racial segregation policies. These policies forced, specifically black men into migrating from rural agrarian communities to work in the country's gold mines (62). Accommodation was provided for these migratory workers in mine hostels, with a change in nutrition, combined with exposure to silica dust in the mines and living conditions that encouraged the spread of TB (47,63,64). In his book, the 'Three Letter Plague', Johnny Steinberg argues that the emergence of HIV at a time when family social structures were being eroded due to apartheid policies, contributed to the unprecedented spread of the disease and its devastating impacts (62). The deadly synergy between HIV and TB was thought to be a result of HIV suppressing the immune system by attacking CD4 cells, this suppresses the body's healthy response to TB bacilli which is to encapsulate the bacteria, and allows TB to disseminate more rapidly and with higher associated mortality rates (65).

2.3 Socio-political context and financing to support TB policy

Contrasting policies related to TB control with those for other diseases, it is striking how under-resourced TB control interventions have been historically, despite the high mortality rates associated with the disease (47). This dichotomy was explained by Phillips (2012) who contrasted the responses to the TB and polio epidemics in South Africa. Between 1918 and 1962 fewer than 950 people died from polio in South Africa, though the crippling results of polio lay in those left with pronounced physical disabilities. The disease preferentially affected the country's "small but powerful and articulate middle class" as described by Phillips (65: 106). In contrast, during the same period, 29 964 TB deaths were recorded in the city of Cape Town alone (54). In South Africa, the history of TB (like that of HIV) shadowed changes in social structure. Evolving public policies (Apartheid) towards racial segregation in South Africa were gaining traction, whereby white South Africans were favoured socially and economically. These policies intensified following residential segregation imposed during the Spanish flu epidemic of 1919 (66: 103). Apartheid policies promoted rural poverty, inadequate health services to most of

the population, rapid urbanisation and fostered living conditions conducive to the spread of TB (47,67). Because the poverty line followed along racial lines, TB control was not prioritised (66). The frustration of medical authorities over the failure of TB control measures resonates through this quote from a paper presented at the first Symposium of the South African Medical Research Council's Tuberculosis Research Institute in 1985, as quoted by Packard (1989).

“Since the disease [TB] is totally curable and available control measures are sufficient to combat the disease effectively, the natural course of the epidemic can be altered to a rapid decline. Why then does the problem remain such a serious one?”

Packard (1989)

When examining historical South African national expenditure reports, there is a noticeable shift in priorities from TB control to AIDS care (68). In the 1994/1995 budget, the Reconstruction and Development Programme (RDP) fund was introduced, intended as a mechanism for redistribution of wealth and services, addressing some of the social inequalities associated with the Apartheid system. The RDP fund included funding for housing development, primary health care, but also included earmarked funds for a conditional grant to support TB control. However, within two years (from 1997), this was supplemented by additional donor funding to support strategies to deal with the burgeoning HIV/AIDS epidemic and TB became overshadowed by the prioritisation of the roll-out and expansion of HIV care. At the facility level, the comparison between the well-funded HIV service (largely funded through vertically implemented conditional grants) and the TB service has been stark and there have been calls for improved implementation of TB control strategies coupled with the necessary designated funding support (65,69). This socio-political context is central to understanding TB control strategies and their implementation, as it influences how services are organised in health facilities as well as how health care workers understand and respond to the disease.

2.4 The structure of decision-making in the South African healthcare system

South Africa is the country with the highest levels of income inequality in the world (70). This inequality is mirrored in the organisation of the health system. The South African health system is characterised by two distinctly separate systems; a well-funded private system that provides services to a wealthy minority, and a public health system serving the majority of the population (71). The private healthcare system is funded through contributions made by employers on behalf of employees to private health insurance firms, who then purchases services from the private health sector (72). Services are provided by a network of private hospitals and medical practitioners. In contrast, the public health system provides health services to the majority of the South African population and is funded through the tax system. In terms of governance structures, decision-making power in the health system has been decentralised, with provinces having their own budgets and responsibility for the allocation of resources between competing health and other budget envelopes (73). TB services in South Africa are largely concentrated in the public sector, and where patients did first access the private sector, this was associated with significant delays in TB diagnosis and treatment (74–76).

2.5 Discussion

In this chapter, the historical intersection between TB epidemics and public policy have been discussed. The macro-level factors that influence TB epidemics include structural, biological and institutional factors. Structural factors refer to issues such as poverty, housing and sanitation. Biological factors include how the disease is transmitted, but also our understanding of transmission, treatment and co-morbidities. The institutional rules include TB control clinical guidelines. Identifying macro-level patterns has the potential to illuminate important relationships and assist in predicting future responses.

CHAPTER 3: THEORETICAL FRAMEWORK AND LITERATURE REVIEW

“Programmes are products of the foresight of policy-makers. Their fate though ultimately always depends on the imagination of practitioners and participants. Rarely do these visions fully coincide.”

Pawson & Tilley (2004)

3.1 Introduction

In this chapter, the theoretical literature related to the research question is discussed and relationships between concepts and theories are presented in a theoretical framework. Firstly, the interactions that make up the organisation of health services is explained using economic theory, characterising the relationships as a set of market interactions. This is followed by an overview of theories explaining the behaviour of agents within the health system, with a particular focus on theory related to how agents make decisions in evolving systems. The implications of observed behaviour observed on the design of mathematical models are then outlined. A potential approach is then proposed, further refined in the remaining chapters of the thesis, and re-evaluated in the discussion chapter.

3.2 Economics of the organisation of health services

In developing public policy, economic evaluation is an approach used to assist decision makers in choosing between competing investments (20,77,78). This analytical approach is used to estimate trade-offs in the cost and disease impact of alternative investments. Economic evaluation is an umbrella term and includes specific approaches such as cost-effectiveness analysis, cost minimisation analysis and cost-benefit analysis. Emerging evidence from programmatic evaluations suggest that intervention benefits shown in modelling studies where data from clinical trials were used to derive estimates of efficacy, do not have the desired effects at a population level (79–81). Some have

hypothesised that this is a result of implementation into “weak” health systems (82), however one may argue that facilities within a health system will have highly variable levels of resources, human resource skills mix and configurations of service organisation. Cost-effectiveness analyses often shows how variability in patient characteristics may influence the decision, but there is paucity of analyses that consider how the decision recommendation may differ between health service contexts with different levels of resources (83).

Context may in part be related to the capacity of the health facility. Aragon et al. proposed that the capacity of an organisation or system can be understood in terms of the ‘hard’ capacities such as infrastructure, technology and finances and the ‘soft’ capacities of the system. The ‘soft’ capacities include the tangible soft capacities such as the organisational systems and procedures for planning; and the intangible soft capacities which include the values and beliefs of agents implementing policies (84–86). In cost-effectiveness analyses we however seldomly include these interactions in our decision-making. How may we incorporate an understanding of the ‘soft’ capabilities of the health system into mathematical models for decision-making? In this chapter, theories of structure and agency in public policy are examined, followed by a discussion of the theoretical foundations of cost-effectiveness analyses, and an overview of approaches to incorporating a more nuanced understanding of the intersection between public policy and the health system in these analyses. In the last section of the chapter, a theoretical framework for analysing the intersection between these relationships is proposed.

The notion of the importance of systems as opposed to a focus on components of health programmes is received increasing attention, with the recognition that priority-setting based on disease specific priorities may result in import priorities being overlooked. The introduction of the Millennium Development Goals (MDGs) in 2000, superseded previous declarations with strong primary healthcare goals, such as the Alma-Ata declaration in 1978 (87). These goals were introduced following the adoption of the UN Millennium Declaration, with countries committing to allocating resources towards these goals for achievement by 2015. The MDGs were a clear political statement on setting priorities for global development. The health MDGs were very ambitious and had specific disease-focused targets (87,88). Those critical of the MDGs were concerned that setting disease-specific priorities would draw attention away from integrated primary

care as incentives follow the targets (89). The task force on innovative international financing for health systems, that evaluated the constraints to scaling up the MDGs, identified ways in which the organisation of the health system would influence how investments may be scaled up (90). They concluded that interventions will be significantly shaped by the context of the health system within which they are being implemented, and that the costs and effectiveness estimates for resource allocation would therefore vary significantly between contexts. In their analysis of the task force's findings, Hanson et al. (2003) distinguished firstly between constraints at different levels of the health systems, and secondly between constraints that may be amenable to buy-out through investment and those that would be more difficult to change, even with substantial investment (91). The authors identified constraints due to governance and policy frameworks as being more resistant to change through monetary investment alone. These constraints may be due to for example, overcentralized planning and management; a lack of inter-sectoral action and partnerships; and government bureaucracy. A commonality among the constraints that are less amenable to buy-out, is that they are related to discretionary behaviour by agents. Constraints that are more amenable to buy-out, would for example include shortages of staff and lack of equipment or infrastructure (91). Classifying constraints by its amenability to buy-out, may underestimate interactions between cross-cutting constraints, making it difficult to predict whether an investment will relax a constraint. Developing a clear causal pathwayⁱ, describing the mechanisms by which constraints and investments are thought to work in the interaction being evaluated, could provide a more nuanced understanding of the constraint and how investments to relax the constraint would operate.

The ability to predict outcomes associated with interactions in systems, whether these are sensitive ecological systems, organisations, or biological systems broadly follows three schools of thought. There is the rational model, which suggests that one can control for the context and study the inputs and resultant outputs of an intervention in a linear fashion, analogous to a pathway through care. In this school of thought, it is then also possible to predict what the effect of the implementation of a standard intervention would be in another context (16). An alternative school of thought is that systems are inherently complex, and that the context is inextricably linked with the processes resulting from the

ⁱ A causal pathway maps the events and interactions that lead to an outcome of interest.

relationship between the inputs and outputs. For this school of thought, transferability to other settings is not possible and interventions should be studied within their own systems. The third school of thought is that, when observing how interventions evolve and influence the systems they are implemented into, patterns can be observed, and lessons can be learnt from studying those patterns. These patterns may therefore be used to understand the transferability of intervention effects (33,92,93). In this thesis, I draw on this third school of thought by attempting to identify patterns of behaviours and to express these mathematically.

When studying changes in systems, the focus may be on macro-level interactions or the focus may be more on the interaction between agents and resources and therefore considering micro-level interactions. When studying macro interactions the behaviour and interactions of institutions or governments are studied as units (94). However, changes in systems often happen because of the interaction between the macro and micro levels, and there with a paucity of frameworks to study such interactions.

3.2.1 The market as a system

Ostrom (1965) defined the market as representing an institutional structure of incentives and deterrents to enable individuals to pursue their own opportunities and at the same time, to perform “socially valuable functions” (95). In neo-classical economic theory, the health system conceptualised as a market, represents the dynamic relationship between supply (healthcare) and the demand for healthcare, with interactions between supply and demand conceptualised as a set of transactions. Adam Smith, introduced the notion that the mechanism governing this interaction is controlled by the price of the product and that if all participants are not satisfied, action will be taken to change behaviour by modifying demand or supply, until an equilibrium is reached (96). This theory assumes that individuals acting within the system are rational and will act to maximize their utility or profit. Apply the notion of systems in equilibrium, the social theorist, Pareto, used the analogy of a pendulum that moves towards equilibrium, for understanding the role of “elites” or the ruling class in the cyclical shaping of democratic governance structures underpinning social change (97). His observations of equilibrium in the system, was that the system is perpetually moving towards equilibrium, and that equilibrium is seldomly

static, but rather a continuously dynamic process. The relationship between the outcomes produced for a given set of resources, is referred to as the efficiency of the system. The market mechanism is considered Pareto efficient, when in terms of the outcomes, we cannot find a way to make some people better off without making someone else worse off (23,98: 5).

The trade-offs associated with the relationship between the available resources and the outcomes produced can be presented as a production possibility frontier, see Figure 1.

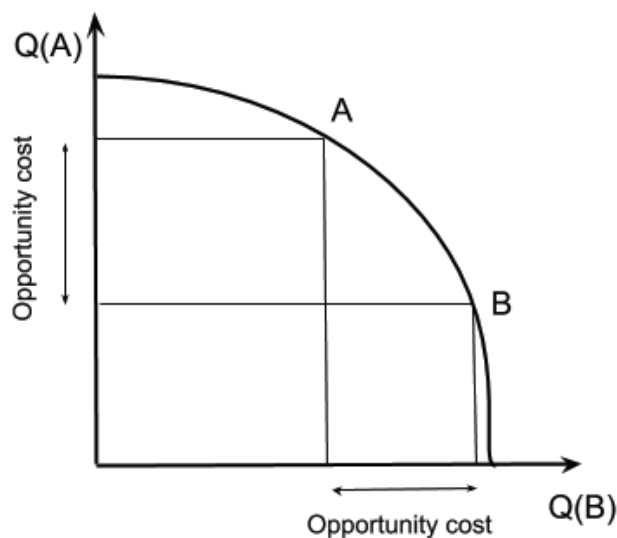


Figure 1. Production possibility frontier. Adapted from Brown & Jackson (99).

The production possibility frontier is a graphical representation of all possible combinations of goods, also called the production possibility choice set, that can be produced with a fixed amount of resources (99). Using the example of two services that can be produced with the same combination of resources, on the y-axis of the graph, represented by $Q(A)$ is the number of TB patients who could be treated with the given set of resources. On the x-axis, the number of children who can be immunised using the same resources is presented as $Q(B)$. Ideally within a health facility, one would like to offer both services. The curve on the graph represents the boundary of the maximum possible output that can be produced from a given amount of input and is called the production function. The shape of the curve is dependent on the technology underlying this interaction. The production possibility frontier therefore shows the trade-offs

between for example seeing y number of TB patients (point A) and immunizing x number of children (point B). The opportunity cost of moving from point A on the graph to point B on the graph is presented by the number of units of $Q(A)$ on the y -axis that cannot be produced in order to produce more of $Q(B)$.

The production possibility frontier as presented in Figure 1 is a simple representation of possible interactions in the market. Philosophically, this understanding of the market is similar to Newtonian ideas of equilibrium, suggesting a cause-and-effect relationship between a force applied and outcomes achieved. If the price is the primary “force” that may be applied to shift the equilibrium, as proposed by Smith, then the constraint to achieving an equilibrium would be a budget constraint (23). However, there may also be non-price rationing factors in health markets that may act as equilibrating mechanisms (100). This is particularly of importance given that access to primary healthcare (including TB diagnosis and treatment) may be cost-free at point of care in the South African public health system, and profit maximisation is therefore seldomly an incentive for provider behaviour. Dor et al. (1987) argues that the time cost associated with accessing healthcare would act as a rationing mechanism by influencing the demand for care in the market, even if care is provided free of charge (101). Non-price rationing mechanisms may therefore include the use of waiting lists or reduced physical availability of services to push the market equilibrium. On the supply-side, production could be transformed by adopting a new technology, by changing the skills mix of healthcare workers, or adding incentives – leading to a shift in the market equilibrium (100). Adopting new technology such as Xpert MTB/RIF (Xpert) for diagnosing TB, would therefore be expected to lead to a shift in the production function, with more outcomes (TB patients diagnosed or reduction in mortality) produced given the same initial inputs, if the resource use associated with Xpert is equivalent to that of sputum smear microscopy.

When considering the production of public services, the production possibility frontier represents what is possible given the current mix and use of the available technology, however this may not represent what is feasible (99,100). Feasible choice constraints are constraints within the current production choice set and represents what is possible without large-scale investment in public health infrastructure or restructuring of the health system. An example of a large-scale investment requirement that may be

considered a feasibility constraint, is that further scale up of TB case finding policies requires access to chest x-rays for those who are symptomatic. However, radiography infrastructure is under resourced in the public health system in South Africa, and therefore would act as a feasibility constraint of the production possibility choice set.

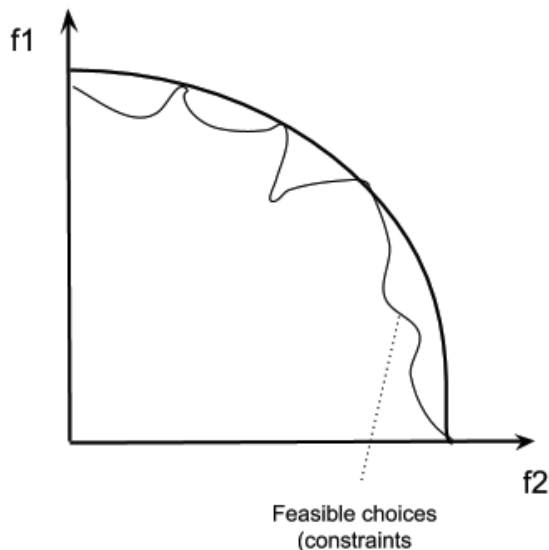


Figure 2. Production possibility frontier with feasibility constraints. Adapted from Brown & Jackson (99).

In Figure 2, the production possibility frontier shown in Figure 1 is redrawn to show how the frontier will be constrained at various levels of the production choice sets due to feasibility constraints. The gap between the feasibility choice curve and the frontier, can be described drawing on two related concepts, x-inefficiency and transaction costs. X-inefficiency is a term used to explain the discrepancies observed in the production of public services when an allocatively efficient mix of services is produced but possibly not at minimum cost (99). This may occur because of overmanning, an inefficient use of technology, or the organisation of services and has been related to the behaviour of bureaucrats. This is likely to cause an upward shift in the cost curve (71: 127, 171). A related concept, though at a micro-level, is that of transaction costs, which speak to the cost of decision-making in a system, especially where consensus needs to be reached on a decision (99,102,103). Within a patient clinical pathway, there are typically multiple decision points, where the way in which the patient interacts with the health system generates the need for decision-making, that may be conceptualised as transactions with

an associated transaction cost. This idea has been applied to understanding the costs incurred by patients prior to accessing appropriate healthcare providers for TB care in Nigeria (104). The authors define transaction costs as the costs incurred by patients in accessing care from inappropriate providers before getting appropriate care. They furthermore argue that these costs are a result of characteristics of the nature of TB diagnosis (possibly harder to change) as well as some institutional determinants of transaction costs, such as the ways in which services are organised. An example of how health services may contribute to transaction costs is when patients are required to return to the health facility to receive the results of their diagnostic tests and if the result is negative, the need to go to another facility to get a chest x-ray, following which they need to return to the first facility for the interpretation of the chest x-ray and formal diagnosis (105). Abimbola et al. (2015) note in their paper, that transaction costs are hard to quantify empirically as they relate to the options foregone because of governance interventions already in place (104). Where others have attempted to conceptualise and measure these costs, it was often done at the proximal levelⁱⁱ and included estimating the cost associated with guideline development, implementation through training and the cost of additional support for the intervention (30,106).

While these approaches are useful to start thinking about the cost of change in the system, it is unlikely to fully represent the costs and outcomes associated with how reducing x-inefficiency in the system may change with time and scale-up. Some have argued that a possible solution may be to consult with policymakers working in the system to rate the efficiency of various interventions in their system (107), however it is likely that policymakers who are entrenched in the system may themselves be influenced by some of the ways of thinking that perpetuate inefficiency in the system being studied (108,109). An alternative approach, and one adopted in this thesis, is to use a processual analytic approach, as described by Pettigrew (1997). He argued that systems are made up of a set of norms and implicit rules and that if one wants to predict how a system may respond to new interventions, one first needs to understand how a system has evolved over time to generate an understanding of the range of mechanisms of change in the system (34,110,111). One may therefore argue that the cost of change (and efficiency foregone) is hard to quantify as it is irrevocably linked to the current organisation of the health

ⁱⁱ The downstream or service level.

system and is therefore dependent on the analyst to imagine how an alternative may be organized. The approach used in this thesis, includes studying the history of TB policies in the system (Chapter 2), and identifying recurring patterns. Secondly, the causal pathways between the interactions the system and the mechanism influencing health outcomes are explicitly depicted in a conceptual framework shown in Chapter 4. The conceptual framework is then used for the interpretation of the model analyses presented in Chapters 6 and 7.

3.2.2 Dynamic systems

Equilibrium theories are, however, not fully able to explain the dynamic behaviour observed in systems. This stems from the recognition that these interactions are more than the sum of their parts and are not merely scaled-up versions of micro-level interactions. Systems tend to display emergent, adaptive and self-organising properties (112,113). Emergence is the notion that when certain elements or parts stand in relation to one another, the whole will have formed properties that are not possessed by the parts in isolation (114). It recognises that parts are influenced by interactions at both the micro- as well as at the macro-levels; while at the same time exerting an effect on the macro-level. This type of thinking has led some scholars to develop theories to study the relationship between the micro-level and macro-level. Notable scholars who studied these interactions include Schelling (1978), Young (1998), Ostrom (1965) and the social theorist Coleman (1986) (113,115–118).

Greenwood-lee et al. (2016) distinguished between complex-adaptive systems characteristics at the macro-level as opposed to the agent (or micro)-level (119). Emergence, considered a systems-level characteristic, he defined as an...

“evolutionary dynamic that describes the process of adaptation that creates change in the ecological dynamic. It is a description of long-term emergent outcomes that result from a utility driven feedback mechanism, in which operational processes and strategies are evaluated, as agents seek to produce better outcomes for themselves. This includes how agents

evaluate and respond to the short-term impacts of the intervention, adapting, and adopting or discarding the intervention accordingly.”

Adaptation, the agent (or micro)-level behaviour, Greenwood further defined as behaviour within...

“a system comprised of intelligent agents, where each agent has a set of objectives and attempts to achieve these objectives through a process of adaptation. In this context, adaptation refers to the process of change that results as various intelligent agents – from policy maker to patient – who modify their behaviour (including any actions required to implement the intervention) and improve outcomes relative to their own perspective and objectives. Thus, although an intervention is designed with one outcome effect in mind, its implementation and impact within the system may deviate from its design because of adaptation.”

This process of adaptation makes the development and evaluation of effective and sustainable interventions difficult and drives the development of increasingly complex interventions. Indeed, interventions must be adaptable both over time and across a diversity of settings to ensure that the adoption and effectiveness of the intervention is not compromised as the population responds to both the direct and indirect changes introduced by the intervention. The high number of linkages between the components of the intervention and the system in which it operates, means that change in the long term, system-level outcomes may be non-linear, emergent and difficult to predict.

The context within which interventions are implemented, influences the implementation and resultant cost and effect of interventions (120). These relationships may be challenging to understand or identify. In program evaluation theory, Gloubermann and Zimmerman (2002), divide interventions into simple, complicated or complex. Simple problems are analogous to baking a cake using a recipe. The recipe needs to be followed, but there is some certainty that if the recipe is followed the results are reproducible. Complicated problems, on the other hand, are likened to sending a rocket to the moon. It is crucial to follow a formula and sending one rocket to the moon successfully provides some assurance that sending subsequent ones is likely to be successful. Complex

problems however are said to be like raising a child. There is no real formula, and being successful in raising a child once does not mean that one would be able to reproduce the success (121,122). Interventions are considered complex when they have a recursive property, change stimulates more change, outcomes and the means to achieve them emerge during intervention implementation (122). Complex interventions may be challenging for economic evaluation because the elements of the intervention and the required inputs may be difficult to identify (123). In multifaceted interventions, it may also be difficult to draw boundaries around the evaluation or in other words, to pin down the scope of the evaluation (123).

In addition to complexity in the intervention, the health system within which interventions are implemented may display elements of complexity (123–126). Theoretical approaches that have emerged for understanding the interplay between health systems factors and the mechanisms by which an intervention works, include complexity theory and a realist philosophy of science. These approaches understand the health system as an open system, in which change is context dependent. Both approaches advocate a greater use of theory to understand the differences and similarities of contextualised interventions (36). In realism, causal processes are understood and identified as mechanisms in the form of context, mechanism, followed by outcome configurations (127). This approach has been critiqued for being too linear, as it investigates aspects of program theory rather than its entirety. The process of a realist evaluation includes identifying mechanisms or causal processes that could explain how an intervention operates. These mechanisms are used to develop what is called a middle range theory, that is then tested against the available evidence in generating an understanding of the mechanisms of actions of interventions (128). This is analogous to the approach proposed by Pettigrew (1990) mentioned above, who suggested an approach for tracking an understanding of how policy has unfolded and been shaped over time, influenced and updated by changes in perspectives and new evidence. The approach is based on the belief that research on how systems change, should “explore the contexts, content, and process of change together with their interconnections through time” (34: 268). Pettigrew argued that the focus for such an approach should be on “catching reality in flight and in studying long-term processes in their context”. He differentiated between an outer and an inner context. The outer context he defined as referring to the economic, social, political and sectoral environment within which the organisation (or firm) is

located. The inner context he defined as the structural, cultural and political environment through which ideas for change proceed.

Complexity theory understands the interactions of processes as local rules that generate patterns of outcomes at other system levels. The local rules may themselves change due to changes in the environment. This is called complex adaptive systems (CAS) and the principles have been applied in policy evaluations for decision making (36,120). Identifying these rules would therefore aid us in understanding how or why certain decisions have been made. Complexity theory therefore lends itself to the study of agent behaviour, while realist theory, allows for the in-depth examination of relationships between outcomes that may include causes other than actor behaviour.

In the disciplinary field of policy analysis, there is a long history of social theorists who have been interested in understanding how innovation (whether technical or social) is adopted and spreads both within and between organisations. Lipsky (1980), for example, provided an understanding of how public policy is shaped by front-line bureaucrats. He observed that the decisions of street-level bureaucrats tended to be redistributive as well as allocative (31). He argued that because street-level bureaucrats must, on a day to day basis, deal with clients' personal reactions to their decisions, they may adapt how a policy is implemented using their discretionary judgement and thereby amending the outcomes of the policy implemented. In a similar way, Gilson (2014) used the symbolism of a prism that refracts the light to explain how organisational culture and management may shape the implementation of policies (27). While the street-level bureaucrats' framework explains changes happening in a distributed and diffused way by those implementing strategies, Rogers (2003), in his work on the diffusion of innovations, discussed the importance of what he calls 'change agents' in promoting implementation (129). He argues that an important factor in the implementation of interventions relates to a person with the ability to inspire action in others, being on board in championing the intervention, leading to widespread implementation.

3.3 Theories of behaviour and agency

So far in this chapter, resource and outcome interactions were discussed as part of a broader system (at the macro-level). A simplifying approach to understanding the system is to break the interactions in the system down into components with independent but connected decision-making abilities, studying how the interactions on these components lead to change.

“...but son, you’ll understand folks a little better when you’re older. A mob is always made up of people, no matter what. Mr. Cunningham was part of a mob last night, but he was still a man. Every mob in every little Southern town is always made up of people you know...”

Atticus Finch, in *To kill a mockingbird* (Lee 1960).

As in this quote of an explanation provided by Atticus Finch to his son in the book, “*To kill a mockingbird*”, complexity in systems, whether social, biological or ecological, lies in the understanding that systems are not merely the sum of the behaviour of individual components of the system (35). Indeed, the system itself regulates behaviour, through rules and norms, but also individuals within the system will, based on their own understanding of the problem or value system, make decisions that sometimes go against what the expressed group decision is.

“Following most evolutionary biologists, we can first ask how a strange behaviour might be adaptive before branding it as irrational”

Jason Collins

Sen (1985) defined agency as “what a person is free to do and achieve in pursuit of whatever goals or values he or she regards as important” (91: 203). Agency is therefore not only determined by the resources (capital) and capabilities of the individual, but also by the capabilities of collectives that the individual belongs to; including gender, ethnicity, and country (131). The range of decision options that agents can action, may be conceptualised as dependent on an ‘option structure’ or ‘choice architecture’ within

which agents act (132). The agency relationship to structure therefore refers both to something material or economic but also has a cultural aspect, relating to norms, customs, traditions and ideologies that govern the behaviour of those in communities. Some of these institutional rules may be negotiable, while others may be more fixed.

While many of the theories conceptualising the relationships between agency and structure portray the agent as a passive victim of the structures (institutional rules and social norms) around them, Unger (1987) proposed the concept of negative capability. He argued that while the constraints of social structure mould the actions of agents, individuals are also able to resist, deny and transcend their context (133). This goes back to the observation made by Atticus Finch when describing the behaviour of a mob (see page 28). The ability to resist rules or social conditioning, Unger called the negative capability of agents. Figure 3 illustrates how the system's characteristics may restrict agents' choices that govern behaviour. In the figure, the individual agent is presented as a black circle on the left of the graph. The range of options that an agent would be able to action on, from an infinite set of options, is represented in the shaded grey oblong – bounded rationality. The notion of bounded rationality is used to explain that people do not always act in ways that may be considered rational from another perspective, because when faced with decisions where there is uncertainty, our rationality (or the range of options that we could consider) is limited by our thinking capacity, available information and time (134). Sen argued that it is not only the ability to make a choice, but also the degree of fit between the available choice and what is acceptable to the agent given his/her values that define empowerment in choice.

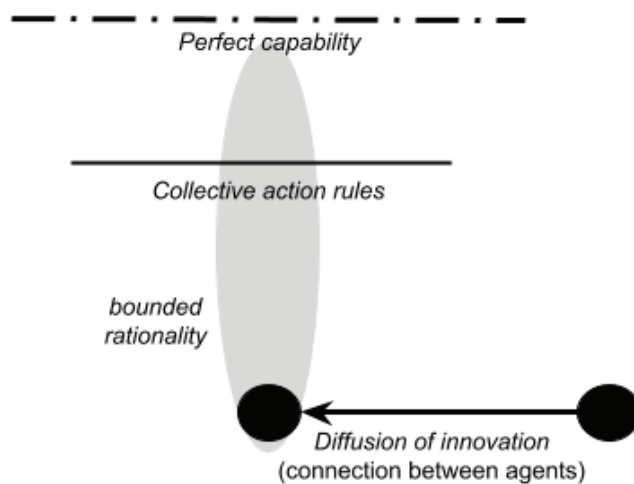


Figure 3. Conceptual diagram representing constraints to agency behaviour.

In Figure 3, this distinction is illustrated by showing the range of agency that an agent can act on (perfect capability) and how this is limited by collective action rules which are the rules set by the society within which an agent functions. The behaviour of individual healthcare workers when involved in the complex task of clinical decision-making, and when interpreting and acting on guidelines, can be conceptualised as being a function of a broader facility-level context, situated within a meso – district level context and within a wider national and global policy-making context (135). It is therefore not only the agent’s internal dialogue but is also influenced by the institutions within which people work and live.

Various economic theory approaches to studying agency behaviour have been proposed, principal-agent theory, game theory and the evolution of the discipline of behavioural economics are briefly discussed in this chapter. Principal-agent theory is used to understand the relationship between a principal (the person who is purchasing services) and the agent (the person doing the work or the person implementing the intervention). Where there is a difference between the best possible outcome for the principal and the consequences of the acts for the agent, this is called ‘agency loss’ (136). Where the agent acts completely in their own interest, agency loss would be very high as opposed to when the agent consistently acts in the interest of the principal, the agency loss will be zero. An example of such an interaction is where health care workers are agents and policy makers are the principals. Policy makers will develop a set of clinical

guidelines, setting expectations for the behaviour of health care workers in clinics. This is similar, in principle to the concept of x-inefficiency. Research using agency theory showed that agency loss can be minimized when the principal and agent have a common interest (i.e. the outcome of interest would benefit both) and when the principal is knowledgeable about the consequences of the agent's activities, minimizing information asymmetry (137). The theory has been criticised for lacking nuance in understanding the motivations of the agent as it assumes that the agent is self-interested and that the objective is to maximize personal wealth.

The need to better understand the nuance of what motivates agents/ individuals in this relationship, and how incentives may be used to change the behaviour of individuals within groups, has led to the development of a field of study that draws heavily on the psychology of human behaviour and interaction, behavioural economics (138,139). When applied to the development of public policy, Thaler and Sunstein (2008) defined approaches that channel people in specific directions while also allowing them some agency (discretion) to go their own way, as nudges (132,140). These nudges work by amending the 'choice architecture' which is understood as the context within which choices are made – analogous to the decision framework shown in Figure 3. The choice architecture is then designed with knowledge of how people make decisions and orchestrated for people to choose a specific option. An integral part of being interested in how nudges may work includes understanding when nudges do not work or may produce even more unanticipated results. Sunstein (2016) identified five mechanisms by which nudges may fail:

- when they produce confusion in the target audience,
- they may have only short-term effects,
- people may resist,
- they may be based on an inaccurate, though plausible, understanding of what motivates people within a certain context, or
- there may be compensating behaviour resulting in no net effect (140).

There is also an ongoing debate on whether nudges in the design of public policy intervention are ethical, with concerns that it may be irreverent of individual choice and

autonomy (141). Within health systems, there is a growing interest in understanding how health care workers may be incentivised to implement policies in specific ways. Some of these approaches, such as target setting, have however been known to cause unintended consequences (142,143)

There are some similarities between the work on nudges and the work done by institutionalist economists who study the behaviour of groups. Institutional frameworks study the rules and relationships that govern the behaviour of groups, and conceptualise organisations as consisting of individuals who interact with one another based on a set of rules that are negotiated between organisations (116,144). Based on these rules observed and studied, one may be able to predict how a system would respond to change. A possible limitation of this approach is that it may conceptualise groups as homogenous and place less emphasis on understanding the behaviour and rationale of the individual actor within the group.

3.3.1 Agents in systems

The literature discussed thus far in this chapter, considers an agent through their interactions with other agents, the next step is to consider how they act within institutions and broader societal systems.

The rational choice model of decision-making suggests that people or institutions will choose to maximise their utility until they exhaust the available resources. However, within collectives (societies or institutions), the rational decision-maker may be more complex as the utility for an individual maximised may not be the same decision as aiming for utility maximisation in a group. The work of Elinor and Vince Ostrom aimed to understand how collectives make decisions when facing resource constraints (145). They conceptualised this decision-making as happening based on a set of implicit and explicit 'rules' agreed upon by the collective. This approach draws on human social behaviour, and explores how the group will shape behaviour, but may not hold true in communities where there is low social cohesion or where there are multiple interacting collectives within an institution. Elinor Ostrom, in some of her early work, identified individuals/ agents who would act differently to the collective; she called them public entrepreneurs conceptualising these actors as leaders who shape and change the collective rules for decision-making in absence of profit maximisation as an incentive (117). Ostrom et al. proposed an Institutional Analysis and Development (IAD) framework that considers the action mechanisms as composing of an action area with action situations with participants. The action arena is constructed through exogenous variables which includes the biophysical conditions, attributes of the community as well as rules (146). These interactions lead to a set of interactions and outcomes. Some of the Ostrom's work has similarities to the work of Lipsky, a social theorist who noticed that bureaucrats implementing public policy tend to reshape policies to adapt them to the context within which they are implemented (31). Street-Level bureaucrats are conceptualised as individuals working within an institution, where there is often a lack of resources to follow a policy implementation request (31: 1980). This notion of the individual making decisions within a specific context, was expanded on with the behavioural economic literature, initially conceptualised by among others, Tversky and Thaler. Within this broad body of work, the individual is making choices within a contextual choice set that

may be modified through incentives (nudge), by making it easier to do the ‘right’ thing, or by making it harder to do what would be the first choice (sludge). These theories describing peoples’ behaviour represent a collaboration between the fields of economics and psychology; and have aimed at understanding the psychology behind the choices that people make when presented with a set of options, thereby expanding the idea of rational decision-maker with the aim of maximising their utility.

While behavioural economic literature is valuable in describing the behaviour of agents in decision-making and how people may respond to incentives, there currently seems to be a lack of appreciation for whether decision-makers are empowered to decide, and how individuals’ empowerment to make decisions may be shaped by the structure of the society within which they live and how they interact with their peers (139). The structure of society may be conceptualised as being made up by the formal and informal ‘rules’ of the society or institutions within which individuals interact. An example of how this may impact on the implementation of health policies is that within very hierarchical work environments, agents are likely to have very constrained choices in terms of deviating from the prescribed norms and standards for their role in the organisation. In a clinical environment, it would mean that in such a setting, clinical guidelines especially as related to vertical disease programme implementation might be followed very strictly. Conversely, in settings where there is a scarcity of appropriately trained health care workers, health care workers may adopt roles that they were not originally trained for, leading to unanticipated deviations from diagnostic guidelines. Institutional norms or guidance may also change with changes in the system. For example, when considering the implementation of new technology at a systems level, there will initially be a disruption of the collective decision-making rules providing greater opportunity for more individual decision-making (146).

3.3.2 Implications for modelling health systems investments

As argued above, while acknowledging that the system is more than the parts, Mangham and Hanson (2010) argued that understanding intervention complexity can assist in identifying approaches to overcoming resource constraints and assist in tailoring the implementation approach to a specific context (147). Mathematical modelling is potentially a useful approach for exploring the effects of different factors that impact on

the cost-effectiveness of an intervention (148). However, how to conceptualise and express these interactions is challenging as elements of the system need to be reduced to sufficient simplicity to be analytically expressed. Coleman (1986) proposed a useful approach to analytically linking the macro and the micro context of actors when evaluating changes in organisations or systems, the framework is called Coleman’s boat (115).

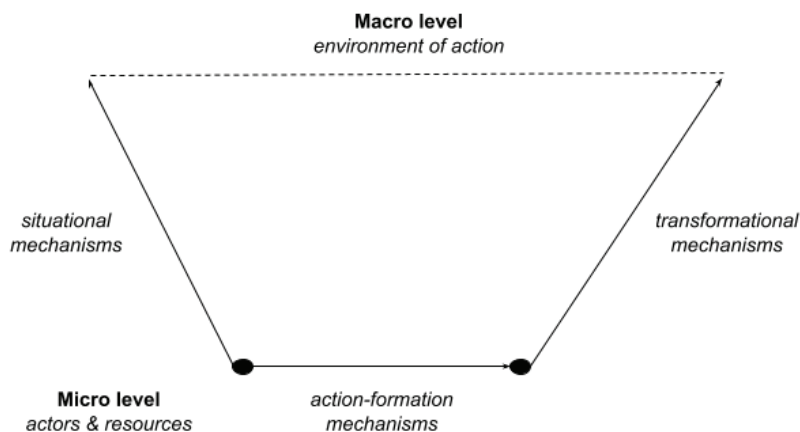


Figure 4. Annotated diagram of Coleman’s boat. Adapted from Coleman, 1986 (115).

Coleman argued that change in systems happens at various levels. At the micro level, actors (here represented as black dots) interact with one another, through what Coleman referred to as “action-formation mechanisms” (149). These mechanisms are those actions that constitute a specific practice leading to the desired outcome (or not). This is the relationship or mechanism, that drives resource use in how patients interact with the health system. The mechanism between the actor and macro level on the left, called the situational mechanism, refers to how the context influences actors. On the right, the interaction between actors and how they influence the macro-level environment is represented, called the transformational mechanism.

Considering the market equilibrium described above: the transaction between agents in the market would represent the action-formation mechanisms, however the role of agents and the dynamic micro-level decision making that contributes to the equilibrium of the system is not only constrained by a lack of physical resources as depicted by the budget

constraint, but also by institutional rules and practices, as well as the limitations in the thoughts and vision of individuals (agency) (150: 3). The institutional rules and practices are expressed through the situational and transformational mechanisms in Figure 4.

Exploring agency behaviour within context has implications for modelling the scale-up of the effectiveness of interventions as well as the associated resource implications of interventions at scale. Coleman's boat may be considered as a methodological framework for representing first the interaction between agents followed by the situational and transformational mechanisms identified and presented in a conceptual framework. Conceptualising constraints to producing healthcare outcomes, through an understanding of agency behaviour and how agents respond to the context, allows us to understand some of the drivers of heterogeneity in estimates of future resource needs as well as the possible effectiveness of interventions. This conceptualisation in addition, presents the opportunity to include an understanding of the incentives and constraints acting on the behaviour of agents in the system and how this may influence the effectiveness and resource use associated with interventions (151). It is therefore a possible approach for identifying policy levers.

Using TB case finding in HIV positive individuals as an example, various factors that could potentially shape the implementation of a program have been identified. These factors can be loosely classified as related to healthcare worker behaviour (supply-side), patient behaviour (demand side), or health system/ infrastructure (supply-side) constraints. Healthcare worker behaviour relates to the actions of those who are responsible for service delivery and their interpretation of the guidelines; Lipsky called these agents street-level bureaucrats when referring to their ability to mould how an intervention is applied (31,120,152). These factors are likely to be influenced by and influence patient behaviour. For example, Lin (2011) identified a decrease in the time between testing and diagnosis as a potentially crucial mechanism for reducing the percentage of patients who will not return to collect their TB test results (153). This would be facilitated by a point of care TB diagnostic as it would negate the need for further visits to the healthcare facility and the associated costs. Health system, infrastructural or programmatic constraints are likely to be another mechanism for influencing both patient and provider behaviour which is ultimately very likely to impact on patient outcomes (105).

3.4 On the theory of economic evaluation

Cost-effectiveness and cost-utility analysis are economic analytic techniques comparing two or more interventions in terms of the ratio of incremental costs per unit of incremental health effect when moving from one comparator to another. The results of the analysis are intended to guide decisions to maximise population outcomes given constraints, most frequently the budget constraint. The way in which the outcomes of the investment are expressed typically defines the analysis. Health economists debate the appropriate theoretical basis for economic evaluation and the implications for how this should be applied (154–157). The two main schools of thought could be summarised as welfarist or extra-welfarist perspectives, especially when evaluating investments that provide a broader range of benefits than health. The welfarist approach aims to maximise societal welfare with a societal budget constraint, is concerned with the distribution of resources, and values all outcomes in monetary terms (158). In contrast, the aim of the extra-welfarist approach is to maximised health outcomes within a resource constrained health system (154,157). Outcome measures are therefore health related. A challenge in the application of the extra-welfarist approach is that using such a framework implies that society is only interested in investing in interventions that will improve health, when many interventions needed to strengthen the health system more broadly may have a lower direct causal link to reducing mortality (158).

3.4.1 Costs and Outcomes

Cost-effectiveness analyses (CEA) uses physical outcomes such as deaths averted, number of patients diagnosed with TB, or life years saved. However, this approach can be restrictive as it is difficult to compare outputs between different programmes. An alternative is the Cost-Utility Analysis (CUA) which uses a multidimensional measure of health as a measure of effectiveness. The multidimensional measures of health include Quality Adjusted Life Years (QALY) and Disability Adjusted Life Years (DALY). The aim of the multidimensional measures of health is to weight the quantity of life by the quality of those years. A limitation of both approaches is that they assume that the goal of the health system is only related to maximising health and therefore that the

opportunity cost in choosing one investment option over another is only related to health (159: 13). However, that may be a simplified way of thinking about the outcomes associated with health care, as one would also be interested in the effect of health care on equity (160,161); how it intersects with social care and the economic burden of illness in the community (162,163). More recently, there have been attempts to expand outcomes to consider the impact of health interventions on people’s capability well-being rather than focusing on health (164). The capability approach has been expanded to the sufficient capability approach which prioritises individuals below a normatively sufficient level of capability with the aim of maximising the number of people in society that achieve sufficient capability, allowing for a more egalitarian distribution of health resources possibly in line with the society’s values.

For each of these approaches an incremental cost-effectiveness ratio is estimated, by calculating the difference in cost between the intervention and the comparator and dividing this by the incremental effectiveness of the intervention. The equation can be written as:

$$ICER = \frac{(C_{intervention} - C_{comparator})}{(E_{intervention} - E_{comparator})} \quad (1)$$

Where $C_{intervention}$ represents the cost associated with the intervention, $C_{comparator}$ is the cost of the comparator. Similarly, $E_{intervention}$ is the effect size of the intervention and $E_{comparator}$ is the effect size of the comparator. The strategy used as the comparator when estimating the ICER, will be the next least cost-effective option when the strategies are ranked (78).

The standard practice in economic evaluations is for cost analyses to include the cost of all inputs needed to produce the required outputs. This is done to include shifts in the use of capital items in the opportunity cost estimation, however this decision implicitly assumes that there is no spare capacity in the system and does not consider the dynamic reorganisation of the health system that occurs with the implementation of new resources (165). Analysts that develop cost functions, quantify these system changes in more sophisticated ways, though do not include the interactions between outcomes and costs. The challenge in these analyses is how to identify the absolute constraints (that cannot be

relaxed) as opposed to constraints that may be relaxed through additional investment (91).

The ICER is then compared against other possible investments to be considered, in a shopping list approach using league tables. The investment with the lowest value ICER would be chosen for investment. Alternatively, the ICER is compared against a cost-effectiveness threshold (CET). Best approaches to estimating the level of the CET are an area of current debate (166,167). There has been a move away from previous suggestions to use the GDP (gross domestic product) of the country, with two broad schools of thought emerging. Some have argued that the threshold should be based on the marginal productivity of the health system and that an investment that is less than this value should be adopted as represents a more efficient use of resources (168,169). Others, conceptualised the CET as a revealed willingness of the health system to pay for an improvement of health, through a deliberative process, revealing certain values and have thus compared the estimated ICER against the ICER of the last decision with a high budget impact that has been made thus putting these decisions in the context of other decisions made (170). This decision, against the threshold, is shown on a decision plane in Figure 5.

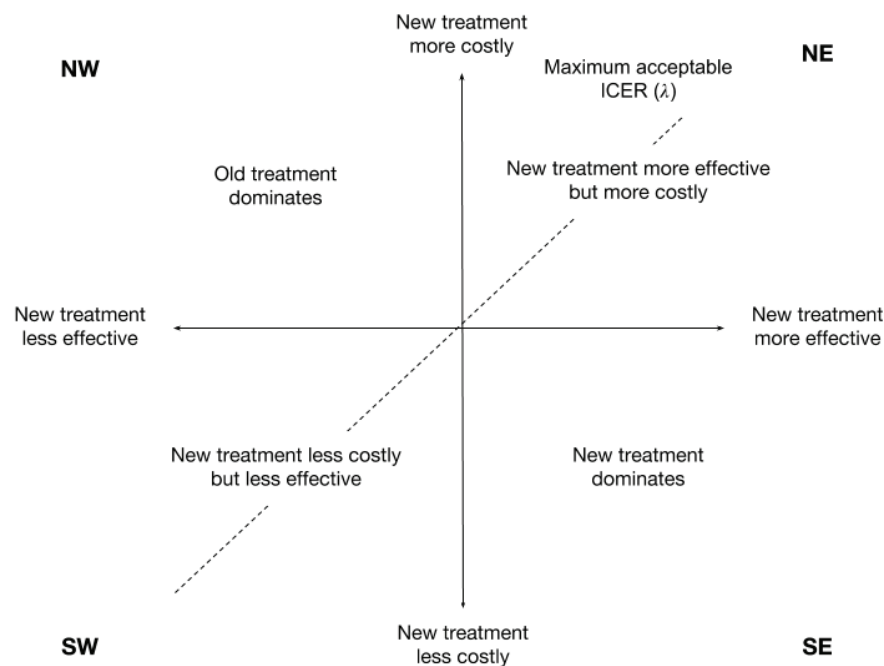


Figure 5. Quadrants of the cost-effectiveness decision plane. Adapted from Briggs & Tambour (171). In the figure, NW refers to the north-west quadrant; NE refers to the north-east quadrant; SE to the south-east quadrant and finally SW to the south-west quadrant. The dotted line crossing through the origin represents the maximum acceptable ICER (incremental cost-effectiveness ratio). An ICER that is plotted

below this line would be considered cost-effective while anything above the line would not be considered acceptable. If a treatment is said to be dominated, it means that another treatment is absolutely preferred. Typically, absolutely dominated options will not be considered for investment.

Following the estimation of the ICER, the decision can be presented on the cost-effectiveness decision plane. This allows for an explicit comparison against the decision-rules, a process for determining whether an investment should be implemented. The plane, plots on the x-axis the incremental effectiveness of a new investment, and on the y-axis, the incremental cost. The ICER of an investment that is more effective and more costly would therefore fall in the top right-hand quadrant of the graph. The decision rule is that an argument could be made for investment if the ICER falls below the maximum acceptable ICER which is represented by the sloped dotted line that crosses the intersect of the graph. If the new investment is more effective and less costly, then the investment is said to dominate other investments and should be implemented. If an investment is less costly and less effective, it may still be implemented, if the reduction in effectiveness is acceptable. Lastly, if the new investment is less effective and more costly, the strategy is said to be absolutely dominated, with what is currently being done being less costly and more effective, and thus the dominated strategy would not be considered. Within a given healthcare budget, investment strategies being considered are seldom mutually exclusive, and what is often useful to policy makers is to present ICER in the form of an investment “expansion pathway”. This is done by estimating each ICER not compared to the base case comparator, but rather to the previous less cost-effective option that is not dominated (172: 329).

In theory, by making decisions based on the maximisation of cost-effectiveness ratios at the margin is necessary for Pareto optimality (22,173). However, in practice, in many low- and middle-income countries, cost-effectiveness analyses are seldom conducted as part of a process of priority-setting across programmes in the health sector, and it is unclear how cost-effectiveness analyses of vertical interventions could fully consider the opportunity cost of not investing in an alternative option; and what exactly the trade-offs are. With many countries now having committed to Universal Health Coverage, the debate has shifted towards the notion of the design of benefit packages based on cost-effectiveness analysis and affordability criteria, as part of a priority setting process (174). In addition, the link between the cost-effectiveness threshold and the budget constraint in the health system is not always clear (175). Some have argued that, beyond the

financial aspects, the budget constraint represents the organisation and capacity of a health system for which the decision is being made (22).

3.3.1 Heterogeneity and decision-making

Governments and donors often want to know whether (and how) investments improve health outcomes, with a focus on the need for ‘value for money’ investments. Decisions made during priority-setting processes that have unintended consequences or where the outcomes from the innovation are not as favourable as was hoped, may have a significant opportunity cost in terms of the value of an alternative investment that was not funded due to the over or under estimation of the benefit or costs of an investment. Decision-making without understanding the context may also result in exceptional value for money interventions not being identified and implemented. Garber (1997) suggested that uniform cost-effectiveness rules applied to a heterogeneous population are unlikely to yield Pareto-optimal resource allocations (176). Cost-saving interventions may be overlooked leading to inefficient and expensive healthcare, or through implicit rationing barriers in access and poor-quality care.

De Sardan (2017) in his criticism of global decision making and target setting shows how interventions promoted by global donors and NGOs are simplified for the sake of widespread dissemination and to promote introduction in an almost identical format in vastly different country settings. He argues that:

“The standardization of public health interventions is still rarely contested, neither at the operational nor at the theoretical level, and as such it appears to be ‘untouchable’. It’s responsibility for implementation failures is neglected, and the major role of travelling models in the ignorance of underestimation of context is largely overlooked”.

An important part of the critique that De Sardan raises, is that merely updating modularized ‘travelling models’ with predefined local variables, will not allow for the insights necessary to make decisions at the local level. Models need to be explicitly built with an understanding of the incentives and motivations that govern the behaviour of healthcare workers and the health-seeking behaviour of patients in a health system

context (177). This approach potentially allows for an improved understanding of leverage points within a system and how strategic investments would need to be designed to support these to improve resource allocation and decision-making in the health system.

Innovations have as a function of their improved utility the ability to initiate change in the health system. Where previous policies or algorithms were not fully implemented, the improved utility or the prospect of improved utility may facilitate an improved commitment to these policies. It may be challenging to observe the changes sparked and these may only become more evident over time by influencing a network of interrelated levels. These may include healthcare provider behaviour, patients' health-seeking behaviour and the wider health system which includes the infrastructure, functional organisation of the system and human resources.

Similar interactions related to decision-making and agency present itself at each level of decision-making in the health system (73,178), whether it is the healthcare worker deciding on the best course of action in the treatment of a patient or the clinic decision-maker deciding how to implement a range of recommended interventions; the district- or provincial level decision-maker tasked with deciding on how to spend the available budget, or decision-making at the national and global levels that shapes the direction of further policy development (32,108,109).

3.4.2 Externalities and sustainability

Up to now, the discussion has focused on how agents and therefore the production function may respond to changes. The market was conceptualised as only related to the health system. However, the health system is itself again situated within multiple dynamic systems. Actions taken within one system that influence other individuals or systems not explicitly involved in decision-making, are called externalities.

In the evaluation of investments for TB control, when conceptualised within the confines of a vertically implemented conditional grant structure, several externalities that may have an impact on other health services should be considered. For example, diagnosing more people with TB, a clear clinical indicator for HIV, may prompt ART initiation and will within the organisation of the clinic, how this could best be dealt with in the existing

services is an important planning function. When considering investments from the societal perspective, the organisation of TB services including the number and duration of visits may affect patient productivity (days unable to work) and contribute to households' medical poverty trap, especially in societies with high unemployment levels. Additional state services, in the form of social welfare may be required to support households. In Chapter 6, we explore how externalities related to the impact of high TB prevalence on informal lending and support in communities may "spread" the medical poverty trap related to Tuberculosis in communities.

3.4.3 Approaches to incorporating aspects of the health system in economic evaluation

An emerging area of debate, especially in the application of economic evaluation in the dynamics and impact of infectious diseases, is that traditionally economic evaluations tend to be static analyses, in terms of the population, the impact of interventions on the population in terms of resource use as well as how guidelines are used. Economic evaluations therefore frequently represent the interactions in the health system at a single point in time (179,180). Within decision-making structures, processes for re-evaluating the cost-effectiveness of investments as changes in the health system happens and the implementation of technologies and the reorganisation of services changes practice (21).

Given the interest in understanding how the system is likely to interact with the implementation of new interventions and the costs associated with these, there have been various attempts at improving modelling methods to make models more representative of the processes that they model (28,153,181,182). These efforts include the development of methods to include qualitative evidence (183,184), allowing for a deliberative process in including model inputs when constructing the model, and for including realist approaches to understanding change associated with the intervention when modelling (185,186). A limitation of traditional cost-effectiveness evaluations is that a simplifying assumption is to focus on the intervention evaluated against a comparator (30,172). However, interventions to improve healthcare do not function within a vacuum and are influenced by healthcare provider behaviour, the socio-political context, co-morbid diseases, the burden of need and resultant patient-behaviour (152,187). As a result, to improve the usefulness of economic evaluations of healthcare interventions, it is

imperative to include some measure of the impact of the context on the cost-effectiveness of the intervention.

There have been attempts at including the complexity of the health system in economic analyses, which often involves mixed methods studies with the results of the qualitative data reported separately in the discussion (188,189). English and colleagues (2009) propose a method for incorporating context by analysing the health system factors surrounding the intervention so that decision makers can clearly consider the context of the evaluation in deciding whether to act on the recommendations (187,188). Barasa and colleagues (2011) note that there are no established methodological approaches to include complexity in economic evaluations and suggest that economic evaluations should take the form of cost consequence analyses with a “balance sheet approach” in which costs and positive or negative consequences can be weighed up for the specific setting. The authors do however note that how this approach would make suggestions in terms of efficiency is unclear (30). This is because it is difficult to predict how resource use in the facility may shift, and which other services are likely to be deprioritised, and therefore the opportunity cost is unclear.

The key methodological debates when applying economic evaluation to health systems strengthening interventions, include:

- Health systems interventions are adaptive and dynamic as it diffuses through the health system, this is partly due to the discretionary power of health care workers in implementing these interventions.
- Many cost-effectiveness analyses implicitly or explicitly assume that agents in the health system (health care workers or patients) are rational agents, by parameterising the analysis based on what is possible as opposed to what would happen in real health systems.
- Decision rules are to implement the strategy leading to the greatest health improvement as the outcome of interest, however intermediary outcomes speaking to improvements in process may be more appropriate for evaluating investments in health systems strengthening.
- Time preference. Investments that strengthen horizontal rather than vertical processes may not show an immediate (within a trial evaluation period) outcome

and the benefit of the investment may only be realised over a 10 to 20-year time period.

- If decision-making were implemented as part of a continued process, there is a need for methodological clarity on approaches for making the case for disinvestment, as part of a dynamic health system.
- Similarly, there is a need for considering when during the implementation of a new investment, it should be evaluated given the need for the intervention to first diffuse through the system.

3.3.4 Spill over effects

Historically, TB has been linked with poor living conditions, poverty and deprivation. Poverty and deprivation may be conceptualised as either absolute or relative, and further conceptualised in various ways. Traditionally, poverty has been assessed simply as a money-metric phenomenon. Increasingly, however, there is a recognition that poverty is a multi-dimensional manifestation of insufficient well-being which includes both monetary and non-monetary indicators. Some of the non-monetary indicators that have been considered include the lack of opportunities, freedom, information, health care, time, etc. and the inability to change this (190,191). The conception of poverty or deprivation (including the multidimensional measures) tends to ignore the relational and interactional aspects of individuals with their community (ecology). Therefore, poverty is often described as resulting from an individual's endowment and social network and not the ecological environment that relates to "civic participation, norms of reciprocity, and trust in others, that facilitate cooperation for mutual benefit" (192: 1 491). The latter is contained in the social capital discourse.

TB is by nature a social disease, given the association with deprivation and transmission through shared spaces (droplets). In addition, poverty is entrenched when those who are ill are unable to work for an extended time, leading to loss of income, and further driving the cycle of impoverishment (52). TB may lead to stigmatisation of patients and isolation from their households and communities (193) due to the infectious nature of the disease thus eroding their connection with others. As a result, the link between TB and

deprivation needs to capture the ‘social’ dimension. For example, Barnes (1995: 10) writes that an attempt to:

“single out the determinant factor or factors in the incidence of tuberculosis ... must inevitably run against the only indisputable fact that emerges from all the available evidence: the lives of many tuberculosis victims were lived inside a constellation of social conditions that affected their overall well-being.”

The costs associated with ill health have been quantified in a variety of ways depending on the conceptualisation of the decision to be made and whether affordability of the cost of illness is considered at the individual, household, ‘firm’ or country level. The resultant costs are either separately considered in a policy decision-making frame or combined with provider costs in an economic evaluation of interventions to support decision making (194: 4). However, these frameworks for considering the burden of ill health are too restrictive as they only consider the costs on individuals and households, without including the impact on the patient’s social networks. Traditionally, the household has been conceptualised as the geographical unit, in terms of those who live in the same house with the underlying assumption that this is how resources are shared (195). However, studies have found it difficult to predict households’ resilience to cost of illness, suggesting that there are factors other than the magnitude of costs at play (196). Recent patient cost studies have found that patients report that they had to borrow money to pay for health care related expenses but that no interest was charged on the loan (195,197–199). These differences are thought to be dependent on social support structures such as being able to borrow money without interest, or where community members are able to perform the role of caregiver, social capital. Household resilience was however found to diminish as chronic illnesses worsened the economic loss over time (200).

3.4.4 Patient costs and the societal perspective

Studies typically estimate out-of-pocket costs including the cost of transport and fees paid for treatment and compare these against a household’s or individual’s income or a proxy of income (52). In some analyses an estimate of time cost or income loss (i.e. indirect costs), whether to the individual or other family caregivers, is included because these are also drivers of impoverishment (201,202).

In the literature, there is a substantial debate on how time cost should be valued (203,204). The approaches used can be grouped by the perspective of the decision-maker (i.e. the welfare state, 'the firm') or the perspective of the individual or household unit. From the 'state' perspective, the objective is to improve the wellbeing of citizens and to understand the impact of ill health on productivity, irrespective of how that productive time is used. This approach is called the Human Capital Approach (HCA), which attaches a monetary value to time spent being ill and unable to perform tasks; as well as time spent waiting at a health facility (205). The value of this time has varied. One approach to valuing people's lost time uses the 'market' value of their time prior to being ill, in other words pre-illness income. While this approach is useful in advocating for a change in health services to improve access to those who are employed, it favours interventions that benefit those who are actively employed and disadvantages those underemployed or not employed outside the home and especially women (206). Others adjust for this in some ways using shadow prices. For example, the time of a mother who looks after her children at home would be quantified based on the market related value for a child minder (205).

When considering the individual or household perspective; a related measure is to value the opportunity cost of patients' time by asking what they would have done if they were not ill or spending time in the health facility (207). This approach has however been criticised in that valuing the opportunity cost of one's time is based on what "the market" would pay for one's skills and could be seen as unjust in societies where people's ability/capability to acquire these skills is constrained through structural inequalities in access to education (208). It is also possible that such an assumption could lead to a focus on policies that would reduce the time cost of those who are least vulnerable based on their level of education and skill set. An alternative approach is to value the time of all people equally by using the mean income from a sample of respondents; or if not available by using a proxy such as the local minimum wage rate (209). Using the HCA, all time lost due to illness or seeking care would be valued and no distinction is made between productive and leisure time (205,206). This is important as leisure time is crucial to the wellbeing of individuals, and to a productive workforce.

If the objective is to understand the burden of ill health on 'the firm' or the economy, Koopmanschap (1995) has argued that the HCA overestimates the cost of productive time

by not distinguishing between time lost where the individual would have been productive and leisure time; and by not taking into account that individuals are likely to work harder the next day to make up for any productivity losses on the previous day (206). The friction cost method has been proposed as an alternative to evaluate the productivity cost of ill health on 'the firm'. A key argument for this approach is that it recognises that within a company, if an employee is ill, it is possible for someone else to take on their work in addition to their own for short periods leading to minimal losses in productivity. However, if an individual is ill for longer periods of time, a new employee will have to be appointed. In the friction cost method, one would therefore see the cost of illness as the cost of having enough staff so that if one is ill, the work can be absorbed (internal labour reserves) as well as the cost of replacing the person who is ill if there is a longer term absence or the person has died (cost of mortality) (206). The value attached therefore represents the net productivity loss observed. The economic unit of analyses for these approaches has primarily been the individual who is ill, their household and those in their household who care for them.

Several approaches have been used to assess whether costs (OOP and time) incurred when ill are affordable to individuals and households. Some studies examine coping costs (eg. selling assets, borrowing money, children withdrawn from school) (210). Others examine whether costs are catastrophic by comparing the sum of the OOP costs incurred against annual household income, individual income or the household's non-food expenditure (211,212). Another approach is to determine whether this pushes families into poverty or exacerbate existing poverty as measured in terms of how household income compares against the poverty line (211). When these measures are applied to an evaluation of the impact of a single disease, such as TB, it is likely that the impact of this illness within a broader health context will be underestimated (213). This is because many patients with TB will also have other co-morbid diseases such as HIV and diabetes that have already been eroding individual, household and community resilience. Having a specified level where households experience financial catastrophe may, therefore, not fully capture the full context of deprivation due to illness. Some have argued that household Ability-To-Pay (ATP) for healthcare is likely to be dependent on a wider range of factors, including the support received from social networks outside the household and community resilience (214,215). In addition, using a proportion of cost to income to compare against the catastrophic threshold does not consider the higher burden placed on

low income households and communities, arguably the most vulnerable (216). It also does not consider how this burden changes during disease progression from acute to chronic, or migration between households or the possible network of dependents households may have who live outside the geographical unit. It is therefore necessary to expand current measures beyond monetary affordability, to include measures of communities' ability to afford the cost of ill health.

The costs incurred by patients when ill and seeking health care is an important mediator of the effect of health service interventions and is included in economic evaluation (societal perspective) to inform investment decisions. Economic evaluation methodology has been expanded to include Extended Cost-Effectiveness Analysis, where the aim is to consider how investment scenarios may influence the proportion of patients with catastrophic costs or how the costs incurred influence position compared to the poverty line (42).

Methods of possibly extending current approaches to economic evaluation include expanding the costs included in the economic evaluation. For Extended Cost-effectiveness Analyses, where the analysis is dependent on assumptions on the size of the household/ the number of dependents on a salary, one may consider increasing the household size, while holding the income static to explore what effect these assumptions may have on the results. Others have proposed alternative decision-rules or extending outcomes in economic evaluation to take into account the family spill over effects of health care (156).

A possible criticism of the approaches used to value the societal perspective is that it seldomly accounts for the connectedness of the community but sees the individual or the individual within their household without acknowledging the impact of ill health on the wider community/society, though one may argue that by incorporating productivity changes some of the impact on the wider community is included. The productivity loss would however not account for resource sharing within a wider community. Within a community with a high burden of chronic diseases such as HIV, TB, Diabetes etc. it is possible that social support structures will get depleted over time and potentially contribute to impoverishment at a community level. Patient cost analyses and especially poverty impact analyses should therefore take these broader issues into account. Whilst

the traditional application of the societal perspective is relevant in a system with a tax-based social support network, in countries where there is a lack of formalised social support, it is crucial to include the costs of informal support in economic evaluations and decision-making. This will help to avoid shifting the burden of ill health from health services to families, households and informal social support structures.

3.5 Theoretical framework of the thesis

The theoretical framework of this thesis is presented in Figure 6. The framework is intended to provide a shared understanding of the causal relationships among core concepts, some of which are then expressed mathematically in the model. It also provides an overarching scaffolding for concepts, some of which are then explored in more depth and represented in the analytical frameworks proposed for specific analyses. These analytical frameworks include the following:

- Chapter 4: the drivers of healthcare worker diagnostic decision making (Figure 7);
- Chapter 5: the concepts related to the economic burden of disease (Figure 17); and
- Chapter 6: the model analytical framework (Figure 22).

The thesis framework presents the cost-effectiveness calculation as the relationship between resources and outputs; which is mediated by the organisation of health services. The cost-effectiveness of an intervention is then compared against a cost-effectiveness threshold; which can represent either the efficiency of the health system or the revealed willingness of the ministry of health to pay for an improvement in health outcomes. The cost of the production of a component of the service, is expressed as the unit. The ways in which these resources are used within the organisation of the health service to produce an output then makes up the cost of care.

The organisation of health services is guided by the social and institutional rules of the health system; and expressed through the behaviour of agents working within the system. The behaviour of agents within the constraints of the system, is influenced by a range of factors including their empowerment, the legal and institutional rules within which they work, their decision-making within perceived scarcity and their own sense-making of the

world (including ethical values and sense of altruism). The behaviour of agents (healthcare workers) may lead to the adaptation of guidelines and the associated resource use. While adaptation will lead to a change in how resources are used, it will also lead to a change in outcomes. In evaluating a diagnostic test, effectiveness does not directly follow from use but is mediated by the clinical decisions made by healthcare workers to request a test, as well as the decisions made in acting on information provided by the test (these can be conceptualised as the positive – and negative predictive values of decisions). The actions of agents with their own decision-making abilities working within the system, implementing an investment, leads to decisions that may not seem as efficient as was originally anticipated. This difference between the intended – and actual behaviour is called the agency cost and at macro level will contribute to the transaction cost of a system, recognising that at each decision point, there is the opportunity for adaption leading to a divergence from what was originally intended.

The organisation of health services also has cost implications for patients accessing the service. At each interaction with the health service, patients will incur a cost in the form of direct out of pocket costs pertaining to travel, or if patients are paying for receiving health care - the cost of the service or medicines, but in addition patients also pay a cost in terms of their time spent travelling to the facility as well as their time spent in the facility waiting for care. In addition to this time opportunity cost, patients may also lose an income source due to the illness, when patients are too ill to work. These interactions are collectively called the economic burden of a disease and the cyclical relationship between ill health, loss of income, and cost associated with accessing care has been called the medical poverty trap.

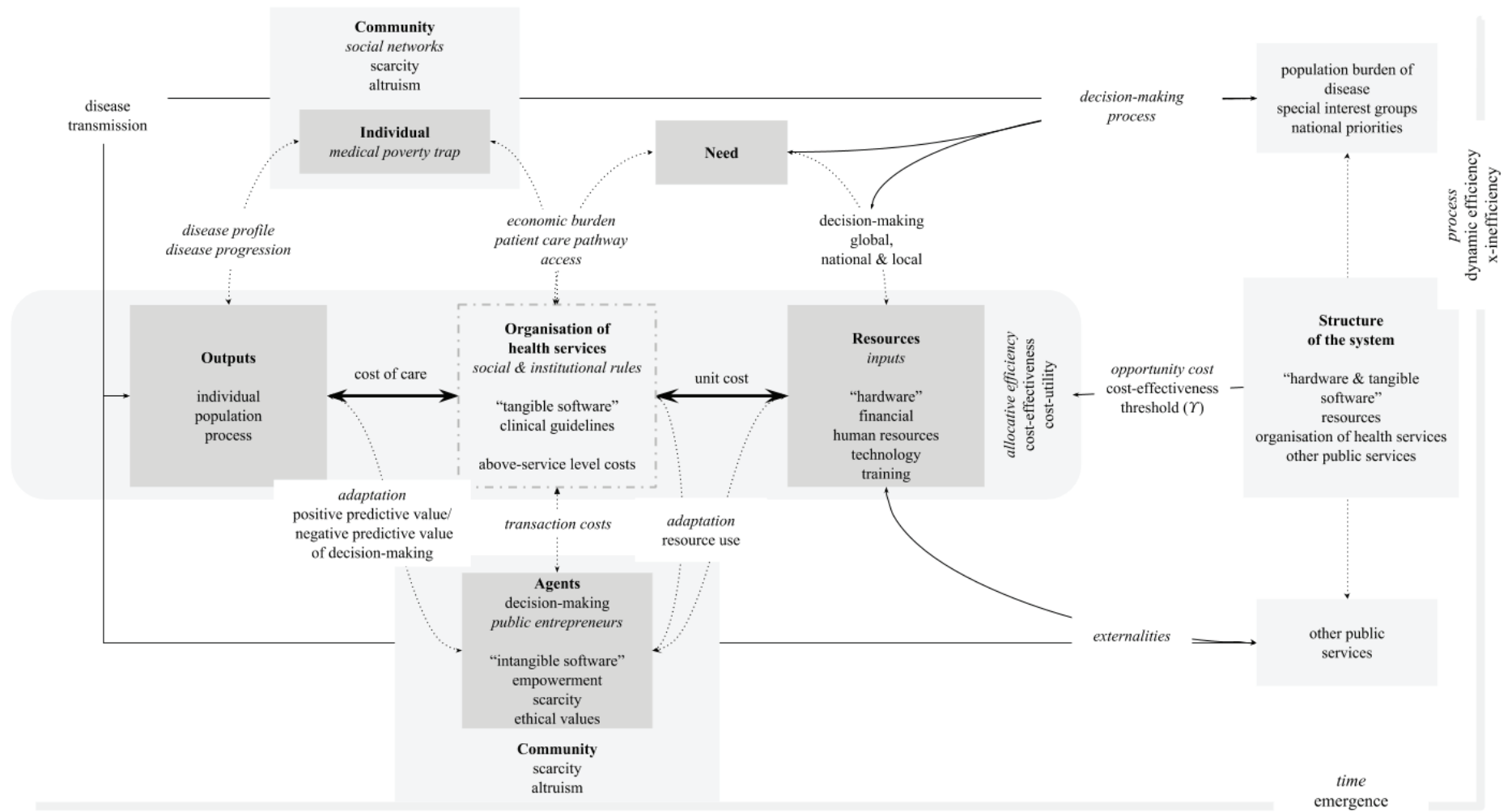


Figure 6. Theoretical framework developed for the thesis.

The need for healthcare, is a function of many interrelated issues. It is not fixed but dynamic and grows and changes with time as is the case of an emerging epidemic, but it also changes as part of political priority setting processes and is sometimes stimulated by special interest groups. In this thesis, we define need for a particular population and then evaluate whether and how that need is met, making recommendations for the best approaches to meet this particular need. Perceived need also, through global, national and local decision-making processes drives resource availability as well as the development of clinical guidelines that ultimately shapes the movement of patients through the pathway of care.

Decisions made within the health sector often lead to outcomes that impact on other sectors. This interaction is called the externalities of the decision. These externalities may be either positive or negative. So, for example, as was explained above, improved health outcomes, will reduce the cost of illness on patients and their households, possibly leading to a reduction in the need for social welfare due to loss of income. Similarly, a reduction in the length of time that a patient is ill or averting the transmission of a disease, could reduce productivity losses of the firm. The scope of an economic evaluation, which relates to the decision on which costs and outcomes to consider in the decision, is therefore a core part of the design and understanding of the problem being evaluated.

Lastly, as the need for healthcare changes over time, so too many of the other interactions will change in ways that are sometimes challenging to predict, given that there are a range of interactions that influence the value of a given service. In economics literature, this shifting is referred to as the dynamic efficiency of the system. Economic evaluation as an analytical tool is used to assess the value of a specific investment at given point in time, within a clearly defined decision framework and therefore does not include these dynamic interactions in order to simplify the decision problem. However, as the practice of these evaluations are being included in the formal decision structures of health systems, there are increasingly recommendations for the cyclical re-evaluation of the cost-effectiveness of technologies. In the next chapter, the design of the economic evaluation upon which this thesis is built, is explained with reference to the empirical – and theoretical literature. In the analytical sections of the thesis, dynamic interactions are included by observing patterns of behavioural interactions and expressing these

mathematically by adding functions to express agency behaviour in the relationships with resource use and outcomes.

CHAPTER 4: METHODOLOGY

4.1 Introduction

This chapter follows on from the preceding chapter, where the theoretical foundations of economic evaluation was discussed, by outlining the methods used in developing the mathematical model that forms the basis of the work presented in this thesis, the SINDI model. The model development will be described firstly by deriving a model conceptual framework to show the causal relationships between the variables included in the model. Parameter estimation is then described, followed by the validation and calibration processes used in the model and concluded in a review of the mechanics of the model using sensitivity analyses (the results of which are presented in Chapter 7) and outlining the strengths and limitations of the modelling platform as well as a reflection on the remaining gaps and areas of improvement needed.

Tuberculosis (TB) is a leading cause of mortality in South Africa (217). The epidemic is associated with poor socio-economic status, nutritional deficiencies and living conditions, as well as with co-morbidities such as HIV and Diabetes. In relation to HIV co-morbidity, people living with HIV (PLWH) have a greater probability of developing active TB, and once ill with TB will have a higher rate of mortality. Furthermore, diagnosing TB in PLHIV is complicated by the disease dynamics. Patients who are HIV positive, are more likely to develop TB in sites other than the lungs (extra-pulmonary TB) and even in those with pulmonary TB, there is less cavitation in the lungs leading to pauci-bacillary sputum samples, making it harder to diagnose the disease when using sputum-based modalities. In contrast, while PLWH have a higher TB mortality rate, those who are HIV negative are currently thought to be more likely to contribute to TB transmission in the community (218), due to the cavitation in the lungs with bacilli expelled when breathing or coughing. Accurately diagnosing TB and starting the appropriate treatment as soon as possible is therefore a key pillar of TB control policy. In 2012, South Africa adopted the Xpert MTB/RIF test as a replacement test for sputum smear microscopy. While in smear microscopy, the bacterium is visualised under a

microscope, Xpert MTB/RIF is an automated system that probes for *Mycobacterium Tuberculosis* genetic material. The integrated platform produces results within two hours and was developed with the potential of being used as a point of care test. In South Africa, during the implementation of the test, it was placed within the existing structure of the laboratory services and as a result, while the turn-around time greatly reduced, it was not reduced to a same-day response. Prior to the implementation of Xpert, most mathematical models predicted that the improved sensitivity of Xpert compared to smear would lead to a reduction in TB-associated mortality at a population level, with similar reductions in TB transmission due to a reduced time in the infectious state (80,219–224). Empirical studies conducted during the roll-out of Xpert showed that the implementation of the new diagnostic guidelines did not lead to a significant reduction in mortality (12,225,226), however many of the studies did show an improvement in intermediary outcomes such as the number of patients with bacteriological confirmation correctly started on treatment. It has been hypothesised that the structure of the health system and the test implementation, constrained some of the potential value of the test in routine care settings (12).

Mathematical models have been extensively used to estimate the prevalence of TB in a population; used to simulate interactions between disease processes and biomedical interventions; to better understand interactions between people facilitating transmission or between populations and biomedical interventions. More recently, mathematical models have been used to simulate patients' interactions within a health system for the estimation of resource needs at the population level (153,219,224,227). However, the majority of these studies used observational data in the form of routinely collected - (228,229) or secondary data from a variety of discrete studies, studying different populations within their context. There was therefore a need to understand within the same population, based on practice in routine care settings, how patients move through the patient care pathway and how this relates to their health outcomes. Cost-effectiveness analyses alongside clinical trials, are used to extrapolate the clinical outcomes from the trial to a period that is appropriate for the decision. It also allows the analyst to explore constraints and the mechanisms by which these may influence the overall results of the decision.

The dynamic modelling of system behaviours has advanced as computers' processing power improved, and modelling methods expanded to include a focus on dynamic models and calibration processes (181). The model structure and approach are typically determined by the question, but an important consideration is also whether macro- (systems-level) or micro-level (between actors) interactions are modelled in a dynamic or static manner. Dynamic models account for both time- and population size dependent changes in the system. While static models consider the system as it would be in equilibrium at a specified point in time, this helps to limit computational complexity in the model. Dynamic models are useful for modelling macro-level processes; however, the complexity involved in modelling multiple interacting mechanisms, and the need to model the intersection between resource use and health outcomes, leads many analysts to use static decision analytic models (DAM) when modelling for cost-effectiveness analysis. In cost-effectiveness analyses the question tends to be, given a set of circumstances described, what would be the best set of investments, within a set budget to address the problem identified. A limitation of static DAM is that they are less adaptable to presenting the dynamic movement of patients into and out of care.

Agent – or individual based models have been suggested as a tool for modelling complex behavioural interactions (230). It is a useful approach to include the detail of variability in patient movements through care. However, these models require large amounts of data, especially when modelling detailed processes such as diagnostic, and are inherently stochastic when modelling the behaviour of individual agents. In addition, including data external to the trial, requires a resampling approach to parameter estimation therefore requiring a very flexible modelling framework and may be very computationally intensive. This makes uncertainty estimation, required for cost-effectiveness analysis, more challenging. Stochastic models include processes that are dependent on random numbers or events, and will therefore produce different results each time the model is run (230: 195). In contrast, in deterministic models, a given set of inputs will always produce the same output. Additional complexity may be added through the inclusion of time-dependent processes in Markov models or the use of cost-functions to present how the production of a service may change with an increase in need (44). In economic models, the effect of changes in resource needs and population on the decision is explored using extensive sensitivity analyses.

We estimate the cost of investments to support the implementation of Xpert, a new TB diagnostic by:

$$P \times E \times C$$

Where P is the probability of movement along the pathway; E is the probability of the event (utilisation) occurring when the patient is in this state; and C is the unit cost associated with the particular service utilised.

This chapter outlines the approach used, and how this was applied empirically. Trials are used as the platform for collecting and analysing data to provide input into policy processes related to resource allocation. Increasingly trials are conducted of, not only biotechnology, but of public health and social policy interventions (231). These economic evaluations have unique challenges and characteristics to be considered in the design of the economic evaluation, especially in cluster randomised control trials or observational studies (232). Firstly, given the expense of conducting trials with repeated follow-up visits, the length of the trial may be shorter than is needed to estimate an outcome for an economic evaluation. Trials are therefore often combined with analyses using mathematical models to predict outcomes beyond the timing of the main outcome of interest collected during the trial. For an economic evaluation, this is often a health outcome, typically mortality. A related challenge therefore with trial-based studies is that the intermediary endpoints in the trial do not necessarily correspond to the outcomes that are most useful to health economists. Decision analytic models are therefore used as a way of presenting a synthesised analysis of available evidence of the causal pathway between resource use and health outcomes.

4.2 Overview of mathematical models of TB diagnosis

Prior to the implementation of Xpert MTB/RIF, mathematical models were used to estimate the possible costs, the effectiveness, as well as potential drivers of revised diagnostic algorithms where Xpert MTB/RIF replaces sputum smear microscopy in a variety of contexts (233–235). As new evidence started emerging of the lack of effect of

the implementation of the revised diagnostic algorithms on population-level mortality, models in conjunction with emerging evidence were used to understand the differences between envisaged and actual impact of revised diagnostic algorithms. Modelling diagnostic processes is challenging, given the need to balance the detailed micro-processes of the diagnostic algorithm that needs to be represented; and the systems-level movements of people into and out of care that drives disease outcomes, while still having the flexibility to investigate the mechanisms of interventions to amend or support these interactions (236). In addition, estimating uncertainty intervals around these detailed interactions can be challenging and may overestimate uncertainty in the final decision (237). In some models, the interactions between the micro- and the macro-level processes, analogous to the interactions mentioned in Coleman's boat, see Figure 4, have been represented by using decision trees to present the micro processes of diagnosis, linked to a dynamic disease transmission model that represents how patient outcomes changes the population in need (224,238). Data sources for the models primarily included data from secondary literature or routinely collected data. Secondary literature tends to be aggregated at the cohort level and may hide interacting variables in the causal pathway that may alter treatment – or health outcomes, these include differing underlying patient, disease and health service characteristics between cohorts studied (239,240).

Lin (2011) developed a modelling framework where he used a transmission model, with smaller transitions to present diagnostic processes. The model was applied in Tanzania and was used to evaluate the effectiveness of Xpert implementation. The model simulations suggested that, within the Tanzanian setting, that Xpert reduces the period of infectiousness from 10.4 months to 9.1 months and argued that the onset of symptoms is not a good indicator of the onset of infectiousness. His effectiveness results were dependent on delays in seeking care (demand side delays), access to TB care (supply side delays), patient loss-to-follow-up before diagnosis, or patients not returning after the diagnostic test, and finally the treatment success rate (153). In a cost-effectiveness analysis, conducted around the same time, Vassall et al. found that from the health service perspective that implementing Xpert would cost \$52 - \$138/ DALY averted. The model also differentiated between new and previous TB and smear positive and smear negative TB. In this analysis, the key drivers of the decision were thought to be the performance of the current TB practice which includes what happens after a negative test result (the

negative pathway). Using the model, they argued that if the sensitivityⁱⁱⁱ of the current diagnostic practice is low but the specificity^{iv} is high, Xpert will have a larger impact on effectiveness, leading to a reduction in treatment costs by reducing the number of people with false positive test results receiving TB treatment. It is possible that following the implementation of Xpert and during routine use, this effect of the reduction of the number of false positives from the test, was negated by the lack of implementation of further tests after a negative test result (negative pathway) – thus reducing the incremental value of Xpert (80).

Gaps in the literature

The following gaps in the literature have been identified:

- The majority of the model-based cost-effectiveness analyses of diagnostics were conducted from the provider perspective (80,219,221–224,241), with the exception of a study conducted in Tanzania (224), as well as the within-trial cost-effectiveness analysis as part of this XTEND trial (79) where the costs incurred by patients were also considered. This is an important gap as the number of visits made by patients in seeking care is likely to extend transmission time, and also increases the costs incurred by patients (104), a potential barrier to health care.
- The model-based analyses typically used data from laboratory studies to estimate the sensitivity and specificity of the diagnostic test, this approach may not fully link the limitations of sputum-based diagnostic modalities to the outcomes experienced by patients. Some of the limitations of sputum-based diagnostic modalities includes poor sputum collection techniques (242), estimates of pauci-bacillary sputum and extra-pulmonary TB (243).

The work reported here, addresses some of these gaps by combining the longitudinal patient cost study, with the provider perspective to also explore how changes in the

ⁱⁱⁱ The sensitivity of a diagnostic test: the ability of the test to correctly identify an individual as having the disease. In a 2x2 table, this would be estimated as the number patients TP/ (TP + FN). Where TP refers to true positive and FN refers to false negative.

^{iv} The specificity of a diagnostic test: the ability of a test to correctly identify an individual as disease free. In a 2x2 table, this would be estimated as the number of patients TN/(TN + FP) (371).

organisation of health services (through changes to guidelines or the behaviour of agents) would shift costs onto households or alleviate the economic burden of TB disease.

4.3 Model structure

The structure of a mathematical model represents our understanding of the relationships and interactions represented in the model. Following a similar approach to what was used by Carter et al. 2018, variables in the analysis were identified from a combination of a review of the literature, and empirical analyses of the trial epidemiological and economic data (244). Squires et al. argued that making the process of model development and the relationships between variables explicit, is an important part of rigour in the development of mathematical models. A conceptual modelling framework was constructed based on the available evidence (184,232,245) and is shown in Figure 7. The framework depicts:

- the relationships between variables in the model;
- hypotheses for how investments may be implemented in the model; and
- shows the direction of the relationship between variables when estimating the incremental cost-effectiveness ratio (ICER).

The model presented here, the SINDI model, uses the structure of a decision-analytical model (DAM) combined with Markov processes in order to bring in some of the complexity of how people move into and out of care (246). The majority of TB models reviewed either used a tree structures whereby patients move along the care pathway based on a set of conditional probabilities until either cured or died (80,220,247). Alternatively, disease models were built with the focus being on patient contact patterns or transmission and the complexity around diagnostic processes were often less fully presented, but dynamics over longer time periods are simulated (234,236). Here, the model was designed to make best use of the detailed data available representing routine patient care, by having patients move into and out of care, from diagnosis through to treatment. Changes in the behaviour of healthcare workers when implemented in the model shifts the ways in which people move into and out of care. We used the data from

the trial, representing routine care to parameterise the rate at which patients would move from out of care back to treatment.

The model structure was defined by a set of mutually exclusive HIV disease states and subdivided to account for 1) TB/HIV co-infection and progression of TB disease, 2) diagnostic and treatment algorithms, 3) drug resistant TB strains. See Figure 8 and Figure 9 for the model structure. To accurately present the complexity of TB diagnostic guidelines, transition sub-trees were added to the symptomatic Markov nodes (248). Using decision subtrees allows for the patient's prior history to be considered structurally, mediating the 'Markovian assumption', referring to the tendency of Markov models to be "memoryless" (249). The model simulates individuals' movements between health states deterministically in defined (monthly) cycles, following a cohort from the start of TB symptoms to death or resolution of symptoms.

Transitions between health states are modelled using the following equations. Patients progress between states at constant rate (equal movement at equal cycle lengths) $\gamma_{1,2}$. The transition probability of going from state 1 to 2 in time t , is given as:

$$p_{1,2}(t) = 1 - \exp(-\gamma_{1,2}t) \quad (1)$$

Estimating conditional probabilities, in other words where there is a movement between states that is dependent on the path patients took in arriving at this transition, can be written as a set of Kolmogorov equations.

It is possible for an individual to remain in each state in successive time periods, or to move between health states (and disease characteristics) monthly, dictated by state transition probabilities, and in the initial states, half cycle corrections were used to adjust for timing in the model. Absorbing states have no transition subtree or affiliated jump state and therefore the probability of exiting the state is zero. The model was developed and implemented using TreeAge Pro software. The model follows on earlier TB economic models but with a focus on explicitly modelling the interactions between patient pathways and the patient-important outcomes of the challenges experienced in health systems (80,153,224,234,250,251).

HIV/TB co-infection alters the rate of progression of TB disease but also dictates the sensitivity of the diagnostic tests and, due to low bacillary load, reduces the ability to diagnose TB from a sputum sample. Three subcategories were created to account for the differences in disease progression, utilisation, diagnostic – and treatment algorithms of those, HIV negative, HIV positive not on ART, and HIV positive on ART. Patients in the model are therefore at any time categorized by the combination of their TB and HIV (on or off ART) status. Each of the five core health states, namely TB symptoms, out of care, Drug Sensitive (DS) treatment, Retreatment, and Drug Resistant (DR) treatment are replicated for each of six possible HIV and TB categories namely HIV negative no TB, HIV negative with TB, HIV positive no TB, HIV positive with TB, HIV positive on ART no TB, and HIV positive on ART with TB. These states are then expanded into 81 unique health states in the model. Patients' transition between model states and subdivisions are based on transition probabilities. Where transitions over time did not occur at a constant rate (time-varying), tunnels linking to parameter tables as well as cost curves were used to represent the change over time in the model. It is possible, within the model, for an individual to transition from being HIV positive to HIV positive on ART, however, within the model, we do not allow those HIV negative to become HIV positive.

The model structure is shown in Figure 8 and Figure 9. All individuals enter the model as symptomatic; receive an initial diagnostic test, followed by additional tests and/ or treatment. If the individual does not start treatment within the first month of a diagnostic test result, they will move to the 'out of care' box in the model and return to treatment at a time dependent function calculated from the empirical data.

Each health state is associated with resource use, costs and a disability weight based on the group's TB and HIV disease profile. The model is used to estimate the expected value of mortality, cost and Disability Adjusted Life Years (DALYs) averted from time in health states to the end of a single TB episode. TB and HIV- associated mortality was sourced from secondary published sources in South Africa and calibrated to the 'within trial' observed mortality rate. Disability-weights were derived from the 2010 global burden of disease study. All future costs and benefits included in the study, were discounted at 3%, and varied between 0 and 10% in the univariate sensitivity analysis.

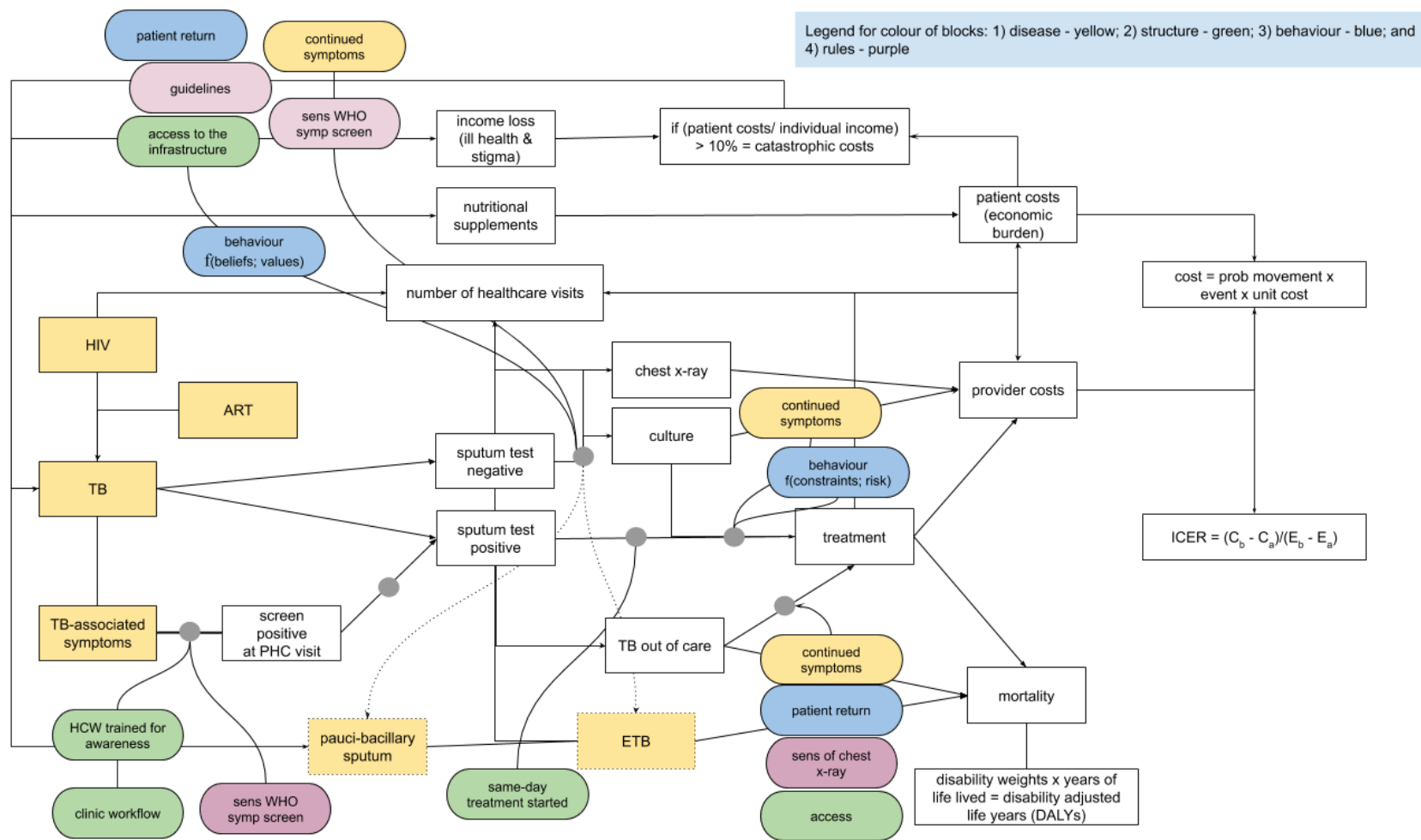


Figure 7. Conceptual framework summarising the evidence used to construct the mechanisms of the model.

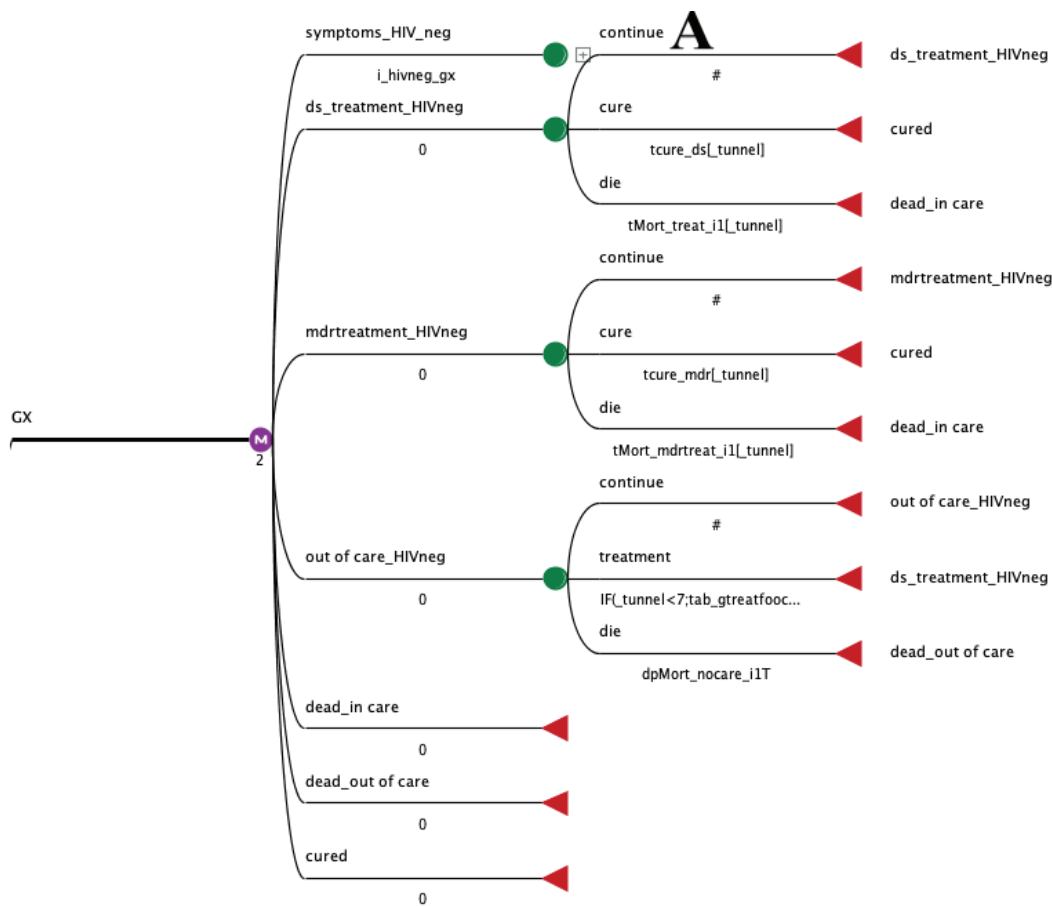


Figure 8. Outline of the Markov processes of the model

This same structure shown here for HIV negative patients with TB, is repeated for patient groups who are (2) HIV negative no TB; (3) HIV positive with TB; (4) HIV positive no TB; (5) HIV positive on ART no TB; (6) HIV positive no TB. The structure shows the part of the model where patients enter the model on the left, move through the health states and the red triangle at the end of the branch represents a movement to the next cycle and state. Where no link to a next box is indicated to the right of the red triangle, those branches are absorbing states, in other words patients do not return to the model population after having entered that state. In the figure, nTB refers to no TB; rr treatment refers to Rifampicin resistance, leading to MDR treatment; and ds treatment refers to drug-sensitive treatment.

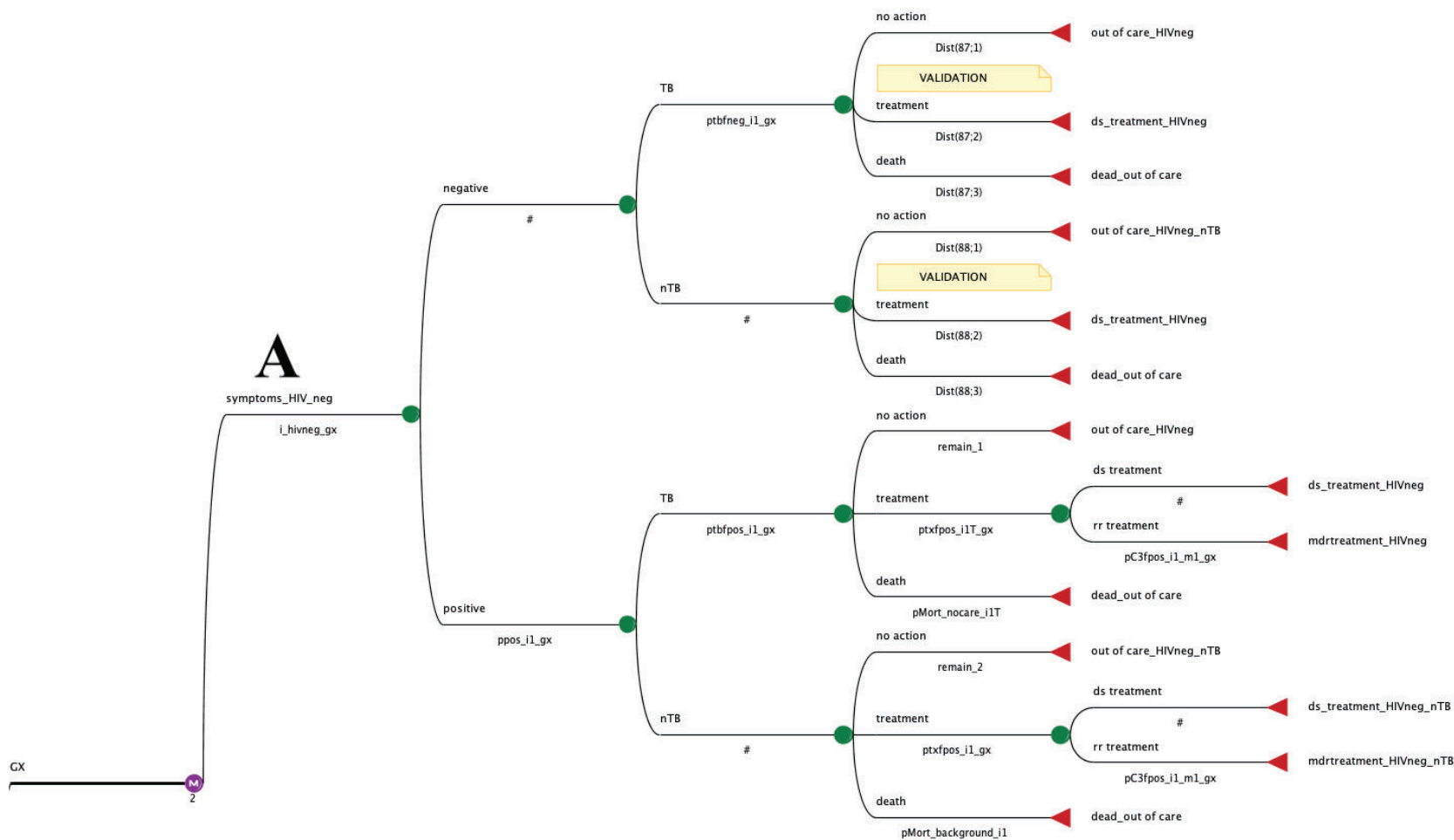


Figure 9. Decision tree structure, representing the diagnostic processes of the model through which an individual enters the Markov states depicted in Figure 8. Where nTB refers to no Tuberculosis; rr treatment refers to treatment for Rifampicin resistance leading to MDR-TB treatment; and ds treatment refers to drug-sensitive treatment. The variables below the line of the tree structure denotes the name of the parameter driving movement through the model. The structure shows the part of the model where patients enter the model on the left, move through the health and process states and the red triangle at the end of the branch represents a movement to the next Markov cycle and state. The states transitioned to are shown in Figure 8.

The outcomes from treatment modelled are cure or death. In order to simplify the model structure, we assume that those remaining in care at six months on drug-sensitive treatment are cured of the current TB episode and would return as a new patient if they become symptomatic again; while those still alive on drug-resistant (DR) TB treatment at 24 months are considered cured. These assumptions follow practice of identifying patients failing treatment earlier in the care pathway, and not having the technology to diagnose sub-clinical TB thus patients with previous TB, would therefore enter the system and be counted as a new TB treatment episode.

4.4 Characteristics of the population modelled

Following common practice in economic evaluation, we use a cohort modelling approach whereby we model options for the care of a particular group of people (cohort). The population modelled is representative of the population of the XTEND study (12), which can be argued to be nationally representative of routine care settings in South Africa.

XTEND was a pragmatic cluster randomised control trial, embedded in phase three of the national roll-out of Xpert in South Africa. Clusters were defined as a laboratory with two affiliated healthcare clinics. Twenty laboratories were selected from four provinces, and randomised to sputum Xpert (immediate implementation) or sputum microscopy (deferred Xpert implementation) study groups (12).

- Provinces represent very rural settings such as the Eastern Cape and highly urban settings such as Gauteng.
- Patients were eligible for enrolment into the study if older than 18, not on TB treatment, and resident in the area for the next eight months.
- If clinic staff requested a sputum specimen to investigate for possible TB. We therefore sampled patients after health care workers, practicing routine care, had already identified a patient as possibly having TB.
- Patient management was conducted by clinic staff in line with routine practice. Participants were enrolled into the study and interviewed again six months later to

determine whether and when TB treatment or anti-retroviral therapy (ART) was started.

- Deaths were recorded through reports from clinic staff, participant-nominated contacts, and by accessing the Department of Home Affairs vital statistics database.

The epidemiological burden and health system indicators relating to TB and HIV care in South Africa are summarised, by province, in **Error! Reference source not found.** and Table 5. The provinces from which the XTEND study was sampled are highlighted in the table to facilitate comparison. The provinces included as part of the XTEND study and thus the population modelled, had a slightly higher HIV prevalence than the South African average, a slightly higher TB death rate among those who were diagnosed, with loss-to-follow-up numbers and treatment success rates similar to those reported as the national average.

Table 1. Epidemiological and health service indicators at the time of the study.

Indicator	EC	FS	GP	KZN	LP	MP	NC	NW	WC	All
Epidemiological indicators										
HIV prevalence (2012)	12%	14%	12%	17%	9%	14%	7%	13%	5%	11%
TB cases reported (all types 2014)	52 734	17 584	46 995	91 382	17 355	18 820	9 001	20 759	45 563	318 193
Proportion diagnosed Extra-Pulmonary TB	6%	12%	13%	14%	13%	8%	4%	8%	11%	11%
MDR-TB cases lab confirmed (2012)*	2205	390	1198	6630	266	760	373	267	2072	14 161
XDR-TB cases lab diagnosed (2012)*	477	31	50	754	3	3	72	10	145	1 545
TB death rate of those diagnosed (2013)	9%	11%	6%	6%	11%	8%	9%	10%	4%	7%
Health service indicators										
Retreatment ratio of total TB treatment started	4%	5%	4%	5%	4%	4%	10%	6%	19%	7%
Proportion on ART in those TB-HIV co-infected (2014)	89%	76%	78%	75%	75%	90%	84%	75%	77%	79%
Treatment success rate (2013)**	77%	77%	83%	82%	58%	76%	72%	66%	83%	78%
TB loss to follow-up (new PTB sm+ 2013)	8%	4%	5%	4%	5%	5%	8%	7%	8%	6%
Financial indicators										
DHS expenditure per capita in 2015 ZAR (USD)***	\$102	\$99	\$79	\$107	\$120	\$101	\$110	\$92	\$103	\$99

In the figure; *numbers of patients started on MDR or XDR-TB treatment is approximately half of those laboratory diagnosed; **Treatment success rate defined as the 'the proportion of all types of TB patients that were either cured or completed a full course of treatment';*** Average 2015 ZAR/USD exchange rate (1 USD = ZAR15,19), from <http://www.oanda.com/currency/historical-rates/> (last accessed 6 March 2016). DHS: district health system; Results are presented by province; EC: Eastern Cape; FS: Free State; GP: Gauteng; KZN: KwaZulu Natal; LP: Limpopo; MP: Mpumalanga; NC: Northern Cape; NW: North West; WC: Western Cape. (Source: 2014/2015 Health Systems Trust District health barometer: 228; STATS SA publication P0302, P03022015: 7; HSRC 2012 SA national HIV prevalence, incidence and behaviour survey)

4.5 Parameter estimation

Five types of parameters were estimated to be used in the model:

- Conditional transition probabilities along the pathway; estimated from trial data
- Unit costs from the costing component of the study
- Utilisation from the same trial participants
- Disability weights from published literature
- Survival from published literature and calibrated to the model analysis, using the structure informed by the conceptual framework. The relationship thus represents the mechanisms driving mortality in this cohort, with the behavioural mediators explicitly explored.

The parameters used in the model are summarised in Table 11.

4.5.1 Conditional transition probabilities

The model parameters were calculated by estimating conditional probabilities from patient-level cohort data collected as part of a cluster randomised control trial (XTEND). The trial methodology is described fully in Churchyard et al. (2015) (12). Conditional probability $P(B, A)$ is the probability (P) of an event (A), given that another (B) has already occurred. Probabilities were estimated for the specific patient types, including those HIV positive, HIV positive on ART and HIV negative at each time step, based on the model conceptual framework summarised in Figure 7. Following the results of the first diagnostic test, patients' further pathways were calculated based on the observed results and how patients would then move through the diagnostic pathway to treatment. For each transition probability, the mean and standard deviation was estimated from the empirical data. Distributions for binomial events, two possible events at a model decision node, such as transition probabilities and disability weights were implemented in the model as Beta distributions. Beta distributions are continuous probability distributions between 0 and 1. Where there were three or more probabilities around a decision node,

Dirichlet distributions were used so as not to exceed one during sampling (252). Dirichlet distributions are multivariate probability distributions, dependent on a set of Beta distributions. In the model, it allows for sampling from each of the underlying Beta distributions defined around the decision mode, with simultaneous adjustment of the other probabilities so that none will exceed a probability of one. Cost and utilisation data tend to not follow a normal distribution and are typically right skewed. This is because costs typically are not negative and can be very large in outlying cases for a range of reasons, including the organisational structure of the health facility where care is being costed or low utilisation of a facility but similar overheads (172: 254). These skewed distributions were implemented in the model as Gamma distributions.

4.5.2 Guidelines and patient pathways

Clinical guidelines are used as a set of recommended rules for practice in clinical settings. The guidelines are typically part of an evidence synthesis process to determine the most effective or preferred manner of identifying and treating patients with specific conditions. These guidelines can be conceptualised as the organisational rules that govern the behaviour of healthcare workers, with the aim of attaining a certain outcome at the population level.

The South African TB diagnostic and treatment guidelines implemented at the time of the XTEND study are described below. At the time of the study, TB screening was primarily passive in that it depended on patients with symptoms suggestive of TB presenting to the health facility seeking care. In contrast, active TB case finding refers to the process of identifying patients with possible TB based on their risk of having TB, and a diagnostic test is offered. More recently, there has been a global focus on scaling up case finding and in the South Africa, the TB programme has extensively scaled up screening in health facilities.

TB screening: has been primarily passive, as it depends on the self-presentation of persons with TB symptoms to health care facilities, bringing their symptoms to the attention of a health care worker. Following the South African national TB investment

case, there has been a shift in these recommendations towards more active TB case finding.

TB diagnostics: The TB diagnostic algorithm at the time of the XTEND study, is summarised in Figures 10 and 11 below.

TB treatment: Following the introduction of Xpert, there has been a move away from a retreatment regimen. The standard (drug-sensitive TB) treatment regimen is RHZE daily for 2 months (intensive phase); followed by RH daily for 4 months (continuation phase). This is the standard treatment regimen for new and previously treated patients. In the case of extra-pulmonary TB, the continuation phase is prolonged to 7 months. It is also recommended that patients are started on Vitamin B6 (25 mg daily) and steroids are given in EPTB. If drug resistant TB is diagnosed: INH mono-resistant TB – RHZA for 6 to 9 months; any Rif resistant TB – MDR-TB regimen for 18 to 24 months.

Monitoring: All diagnosed with Xpert will also need to have a baseline smear and be monitored with smear microscopy. If smear negative or EPTB, will be monitored clinically. A smear microscopy is done a week before the end of the intensive phase of treatment. If the smear microscopy is positive conduct a LPA (or culture and DST) to check drug sensitivity. Repeat one week before the end of the continuation phase. If positive, patient is identified with treatment failure. Recheck patient's drug susceptibility.

ART: ART initiation if TB diagnosed before starting

ART: if patient has a CD4 count < 50 start ART straight away. If the CD4 count > 50 start ART before end of intensive phase. If a patient develops TB while on ART, continue treatment but adjust the ART dosages to minimise drug-drug interactions.

(About 20% of HIV+ patients who start ART after TB diagnosis will develop TB-IRIS. Prednisone is used to suppress severe symptoms.)

DOT recommendation: The recommendation in the NTCP adult TB guidelines is that patients' treatment monitoring should be adapted in a way such as would most suit the patient.

While the summary presents the official guidelines, these guidelines were not uniformly implemented across all nine provinces in South Africa, with implications for the

generalisability of the results of the model estimates. For example in the Western Cape instead of a single sample, two samples were taken consecutively at the health facility and sent to the laboratory (75). This provided the opportunity for an additional sample to be available in the case the first sample was not viable (low bacillary load or saliva as opposed to sputum) or if there is the need to culture a sample to check for drug resistance. A sample is not reusable after an Xpert test has been performed given that the bacteria is destroyed in the sample as part of performing the test. Therefore, routinely taking two sputum samples, is thought to provide more definitive results, more quickly and reduces the need to request another sample from the patient, which may delay diagnosis.

Comparing against other patient pathway analyses; data collated from the South African national routinely collected data system showed that based on an estimated TB incidence, that of all patients with true TB, 95% access TB tests, 82% receive a diagnosis, 70% get treated and only 53% of those with TB will be recorded as successfully treated (228). The data from the XTEND trial was used to parameterise the movement of patients through care (12). In the trial cohort, 14.9% (26/174) of patients in the microscopy arm of the study and 17.0% (34/200) of patients with bacteriologically-confirmed TB in the Xpert arm of the study did not start TB treatment within 28 days of submitting a sputum specimen. A review of routinely collected data in 11 primary health care clinics in the Western Cape, found an initial loss-to-follow-up of 16% (253). In the analysis of routinely collected data described above, the authors found an arithmetic mean of 19.4% initial-loss-to-follow-up rate with a range in values of between 14.4% and 24.3% (228). The similarities in initial loss-to-follow-up estimates between the routinely collected data and the results from the XTEND cohort thus suggests that the behaviour modelled from XTEND can be seen as representative of the population in South Africa at large.

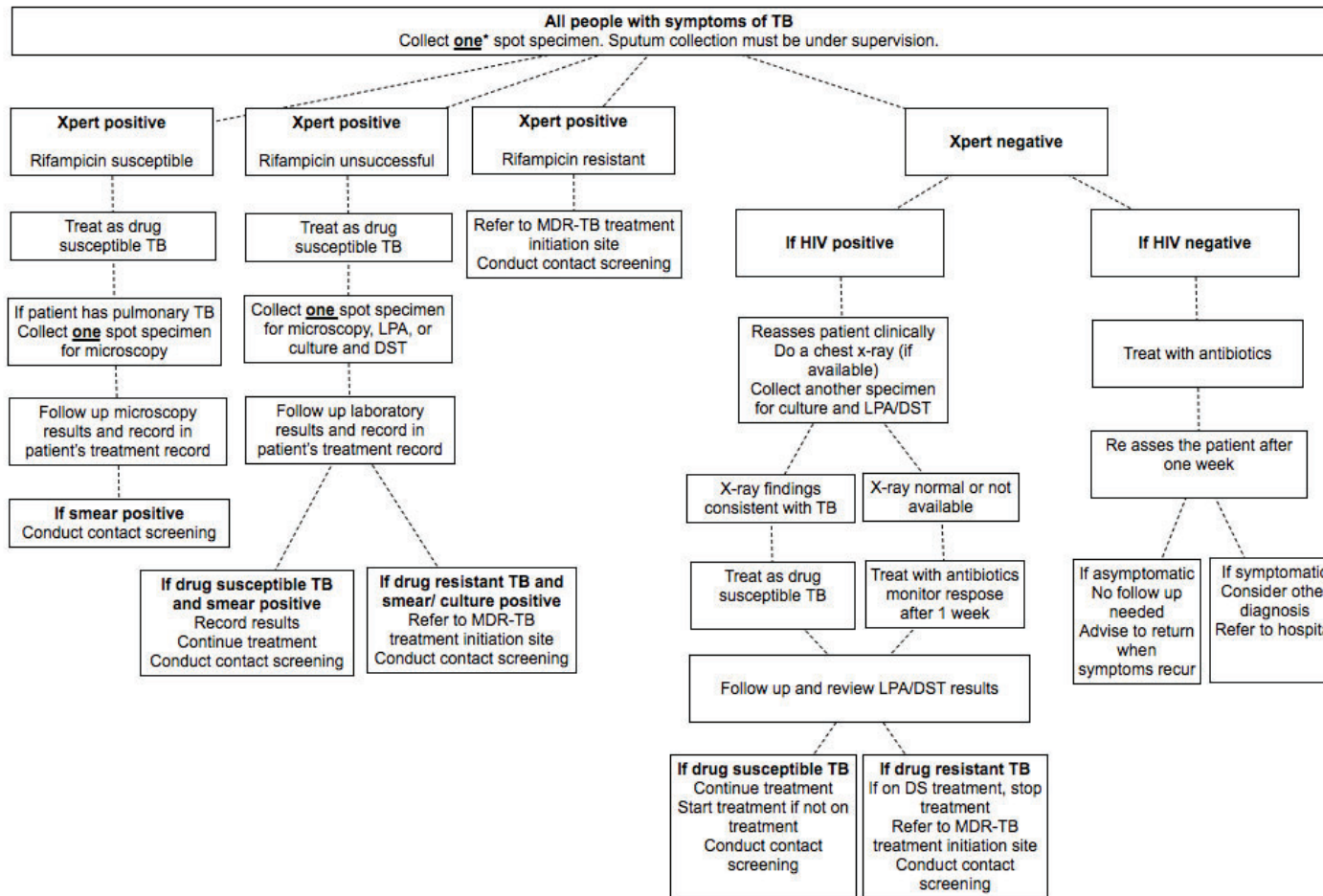


Figure 10. South African TB diagnostic guidelines (Xpert-based) at the time of the XTEND study.

The algorithm presented here, represent the South African national guidelines at the time of the XTEND study. However, since the XTEND study (2012), the South African TB diagnostic guidelines have been updated to include the use of the urine LAM assay in hospitalised HIV-positive individuals with low CD4 counts (NAC, 2017).

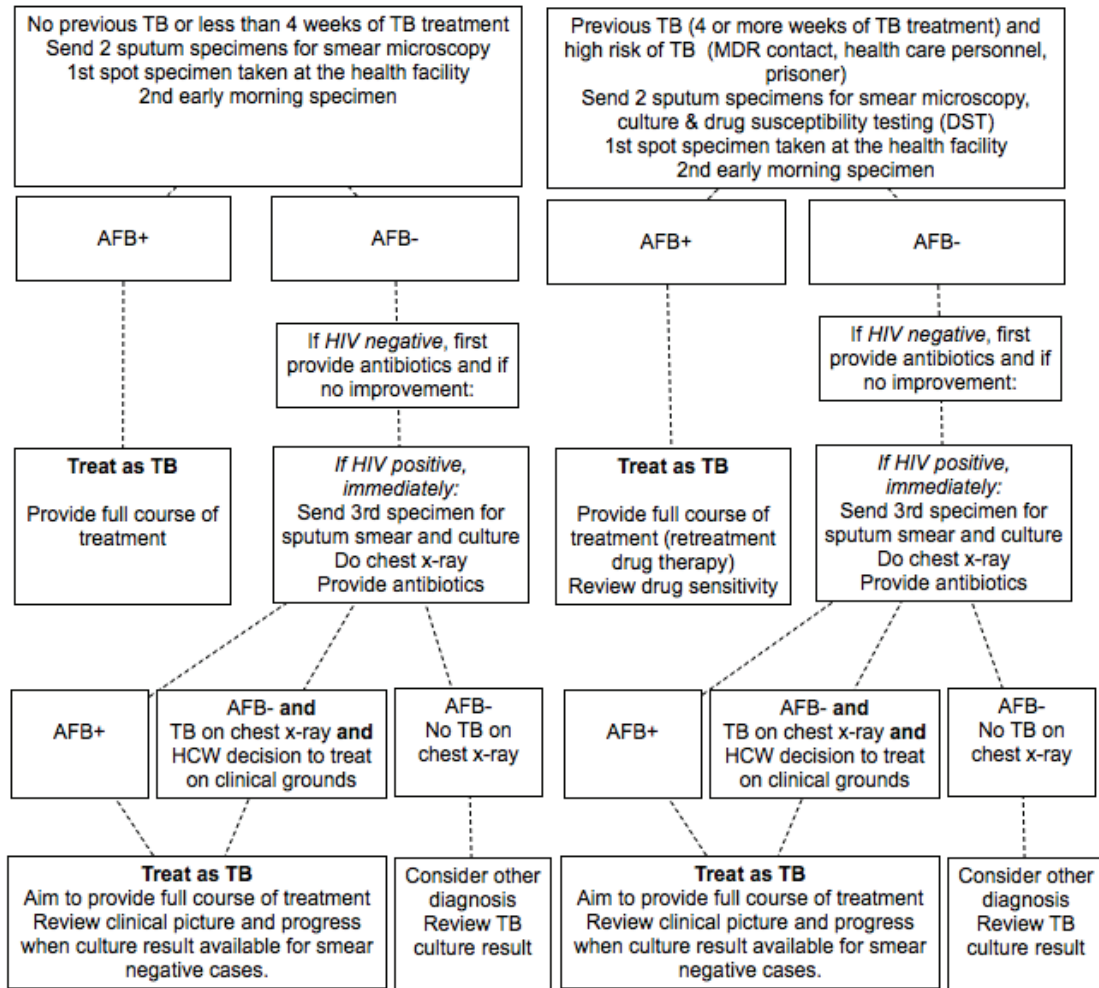


Figure 11. South African TB diagnostic guidelines (Sputum smear microscopy) at the time of the XTEND study.

Table 2: Description of the model of TB service in each of the facilities sampled

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10
Province	Eastern Cape	Eastern Cape	Eastern Cape	Free State	Free State	Free State	Gauteng	Gauteng	Mpumalanga	Mpumalanga
Setting	Busy clinic located in a semi-rural area. Clinic located in town	Very busy clinic in a densely populated area within the town limits.	Rural. Sparsely populated area.	Township setting with the clinic centrally located. Densely populated area.	Township setting. Clinic located at edge of township.	Semi-rural area. Bordering Lesotho. Located on a hill which has access via a potholed dirt road.	Township setting, mining community. The clinic is on the outskirts of the township.	Large very busy clinic on the outskirts of Pretoria.	Rural. Located between scattered dwellings.	Urban. Located in a densely populated area in a township on the periphery of a city.
Annual clinic headcount	53 491	74 294	14 887	65 682	50 077	47 245	87 078	120 589	75 847	82 217
Model of TB service	Patients with possible TB are investigated in the facility. While awaiting test result, patient is treated for a chest infection. Daily facility-based DOTS are provided.	PHC and TB services are integrated. Patients with possible TB are referred to the exclusive TB nurse to collect TB sputum. All TB positive cases are also tested for HIV. TB treatment is collected from the clinic two-weekly. Approximately 10% of TB treatment are on facility-based DOTS.	TB services are integrated into PHC. Approximately 10% of TB patients get daily facility-based DOTS with the remainder on community DOTS.	TB services integrated into the PHC system. Patients with possible TB are screened in the PHC rooms, if a suspect test positive for TB treatment is started and monitored by a professional nurse. TB patients receive daily facility-based DOTS.	TB services integrated into PHC. Patients with possible TB are identified in PHC and sputum taken in the TB room. TB patients collect medication at the facility weekly. Patients living and working on farms are given a monthly supply of treatment.	Patients with possible TB are screened in the PHC system. Facility based daily DOTS is administered by DOTS supporters employed by a local NGO. Daily, facility-based DOTS are provided. Retired professional nurses follow up patients who miss appointments.	Diagnosis is made by a dedicated professional nurse, who then prescribes treatment and monitor patients. Daily facility-based DOTS is provided	TB services provided separately in same corridor as HIV services. Patients with possible TB referred to the TB section.	Patients with possible TB are screened and diagnosed in this clinic then referred to a separate TB clinic for treatment. Integration is in process.	There is a separate TB section with focal nurse. If on streptomycin, TB patients come to the clinic daily, otherwise collect a monthly supply of treatment and seen by peer educators/CHWs four times in a month.
Median intensive phase visits new treatment	4 (2;5)	2 (2;3)	0.5 (0.5; 1)	4 (4;24)	1.5 (1.5;2)	20 (2;20)	17 (4;23)	1 (1;1)	1 (1;1)	1 (1;1.25)
Median intensive phase visits retreatment	18 (4;28)	N/A	N/A	N/A	N/A	N/A	21 (16;27)	N/A	0.5 (0.5;0.5)	2 (2;2)
Median continuation phase visits new treatment	4 (2;4)	N/A	2 (2;3)	1 (1;1)	2 (2;2)	0.5 (0;4)	4 (4;17)	1 (1;1)	2 (1;2)	2 (2;2.5)
Median continuation phase visits retreatment	4 (4;4)	N/A	N/A	N/A	N/A	N/A	13 (4;22)	N/A	N/A	2 (2;2)

In the Table, data collected from the clinic manager between July 2011 and June 2012. Where CHW refers to the community health workers; DOT is directly observed therapy; PHC is primary health care; NGO is non-governmental organisation.

4.5.3 Unit costs

Costs incurred by the cohort simulated in the model is estimated by adding a unit cost value multiplied by the utilisation associated with a specific health state or process during the specified time interval. Costs were assessed from a societal perspective and are reported in 2013 US dollars (USD). Using similar arguments to ones posed by Meyer-Rath et al. 2015, costs were not inflated to present values (255), because adjusting for inflation would not accurately represent the present value of resource inputs given that some of the inputs do not track the consumer price inflation (CPI) index. For example, the prices of medicines used in the public sector are decided through a tendering process and then set for a number of years (256). Similarly, human resource costs are not primarily dependent on inflation-based increases as increases in the salaries of healthcare workers are determined through negotiations between trade unions and the State.

Unit costs were estimated as part of primary data collection alongside the trial, sampled from the same study sites where the outcomes data were collected. The details of the methodology associated with these costing studies have been published (198,257–259). A combination of top-down and bottom-up costing methods were used. So, for example, facility overhead costs were allocated to specific processes using a utilisation or staff time allocation factor. Processes were observed, inputs noted and valued, and interactions timed to estimate the unit cost of a procedure or input (258).

Provider costs, the cost of diagnosing and treating patients with TB, were estimated for eight of the primary health care facilities included in the study (two per province) and included the cost of building health care facilities, the cost of human resources, the cost of any observed resources used and the cost of medication. The cost of medication was estimated from the South African Department of Health medicines price registry, which lists the tender price of medicines negotiated. We added 8% of the tender price of the medicine, to this cost for the distribution system (ref Margaret von Zeil, personal communication). For MDR TB treatment, we followed the estimates of Sinanovic and colleagues who constructed a cost of RR TB treatment by assuming a mixture of centralised and decentralised models of care were used nationally based on a 54%: 46% urban-rural split (259). Inpatient care for MDR treatment was assumed to be 44 days in

the fully decentralised model and 128 days in the fully centralised model. The cost associated with Xpert in the laboratory was likewise calculated from primary data collection in twenty laboratories during test implementation, and includes the cost of laboratory space used to process the test, human resource costs (based on time spent processing observed), as well as the cost of any resources needed to conduct the required assays (258). Provider unit costs estimated are summarised in Table 3.

Table 3: Provider unit costs in 2013 US\$

Description	Value or calculation	Distribution	Reference
Antibiotic trial (5 days) per patient, drug costs	\$0.28	Uniform	Vassall et al. 2017; Churchyard et al. 2015
Chest x-ray	\$15.17	Uniform	Foster et al. 2017.
Culture	\$12.90	Uniform	Cunnama et al. 2016.
Culture (DST)	\$25.10	Uniform	Cunnama et al. 2016.
Inpatient bed day	\$71.61	Uniform	
LPA	\$20.30	Uniform	Cunnama et al. 2016.
Microscopy test	\$8.67	Uniform	Cunnama et al. 2016.
Public clinic visit	\$12.54	Uniform	Vassall et al. 2017.
Treatment visit	\$7.32	Uniform	Vassall et al. 2017.
Xpert test	\$16.90	Uniform	Cunnama et al. 2016.
DS treatment, time-dependent	$IF((0.1809(_tunnel)^5 - 6.9701(_tunnel)^4 + 73.436(_tunnel)^3 - 309.63(_tunnel)^2 + 528.71(_tunnel) - 246.25) < 0; 0.1809(_tunnel)^5 - 6.9701(_tunnel)^4 + 73.436(_tunnel)^3 - 309.63(_tunnel)^2 + 528.71(_tunnel) - 246.25)$	time-varying	Estimated from Vassall et al. 2017.

In the Table, DS treatment refers to drug-sensitive treatment; LPA line probe assay; DST drug sensitivity test.

The costs incurred by patients were estimated from patient exit interviews conducted with two cohorts of patients, in ten of the XTEND study clinics (198,257). The unit of analysis was the patient within their household and community. The first cohort of 351 people with suspected TB were interviewed at the time of receiving a TB diagnostic test and

followed up six months later. The second cohort, 168 patients on TB treatment were recruited from the same ten facilities and followed up at five months on treatment. In addition, 134 RR TB patients at different stages in their treatment were interviewed with 82 of these receiving inpatient care and 52 receiving treatment in outpatient facilities. We estimated health care utilisation, out of pocket costs incurred due to transport and other expenses incurred. We also estimated patients' income and income loss associated with ill health; as well as the cost of informal care. Cost results are presented separately for patient costs and 'community costs' that includes the cost of informal care.

The costs associated with health seeking behaviour and time loss from the start of TB associated symptoms to getting tested for TB were estimated. The number of health service visits associated with receiving health care during case finding and treatment was based on a combination of patient reported (patient surveys), and provider reported visits for each facility.

Where intervention scenarios modelled increased ART uptake, we included a monthly cost of ARV treatment and associated patient costs from secondary data sources. However, we do not include the cost of ART in all comparators. In the trial population, the implementation of Xpert did not increase the proportion of patients starting ART when compared against the smear microscopy arm of the study (12) and it is likely that adding the cost of ART could make interventions that differentially benefit those who are HIV negative appear more cost-effective (due to the significantly lower costs) than interventions that benefit patients on ART, with potential equity implications in the distribution of resources (260).

4.5.4 Events

The use of health services as patients progressed through care was collected as part of the trial through case note abstractions of identified fields in the patient records. In addition, patients were asked specific questions about their use of health services during their illness and care seeking.

4.5.5 Outcomes

A range of outcomes were used in the economic evaluation. The primary outcome from the trial was mortality six months after a TB diagnostic test (12). In the economic evaluation, we were also interested in the process or intermediary outcomes, these included the number of patients started on treatment; bacteriologically confirmed TB; initial loss-to-follow-up; started on drug-sensitive TB treatment; started on retreatment; and started on MDR-TB treatment. In addition, the proportion of patients with true TB was estimated using the model and reported in the results. The primary outcome of the economic evaluation was disability-adjusted life years averted (DALYs), based on global recommendations for comparability across interventions (261). DALYs were estimated by adding years of life diseased (YLD) to the years of life lost (YLL). YLD is estimated by multiplying the number of cases by the disease duration and the disability weights. Standard disability weights from the Global Burden of Disease study were used (see Table 11). YLL was estimated by multiplying the number of deaths by the life expectancy at the age of death (in other words the number of years lost due to premature mortality). For the average age of onset of TB, the average age of the TB cohort interviewed (38.16 years) was used (81). The remaining life expectancy at age of onset of TB was estimated by subtracting the average age of onset of TB (38 years) from the average South African life expectancy at birth (63 years^v) (262). We assumed that disability weights are not additive but used the highest disability weight where more than one disease was present.

^v This was estimated by taking the average of the estimated life expectancies for 2012, 2013, 2014, 2015 and 2016 as reported in the SAMRC rapid mortality surveillance report (262).

4.6 Validation and calibration processes

A recent systematic review of model-based cost-effectiveness analyses of TB management found that when comparing models, their processes and outcomes, and their influence on outcomes and conclusions, that there were vast disparities in the structure of models and this structural uncertainty contributes to variation in estimates. The process of model validation against observed outcomes reduces structural uncertainty in models by refining the model structure and covariates used in the model (263).

The economic analyses conducted as part of the XTEND trial, included a ‘within-trial’ analysis using statistical methods (233). The objective of the ‘within-trial’ analysis was to test whether the implementation of Xpert made the TB diagnostic algorithm in South Africa more – or less costly than the sputum microscopy-based algorithm. This analysis was restricted to the 6-month period of the trial follow-up. The model reported here, SINDI, was developed to extend this analysis to identify where in a patient’s entire TB episode (36 months) would further investment in the diagnostic pathway improve the value of new TB diagnostics; with the aim of better understanding the interaction between resource use and patient health outcomes.

Structural uncertainty in the model was minimised by validating the outcomes of the mathematical model to the statistical analysis as part of an iterative process that led to a refinement of the model architecture. This process allowed for the identification of possible model programming errors, as well as to identify differences in assumptions between the two analyses.

4.6.1 Validation

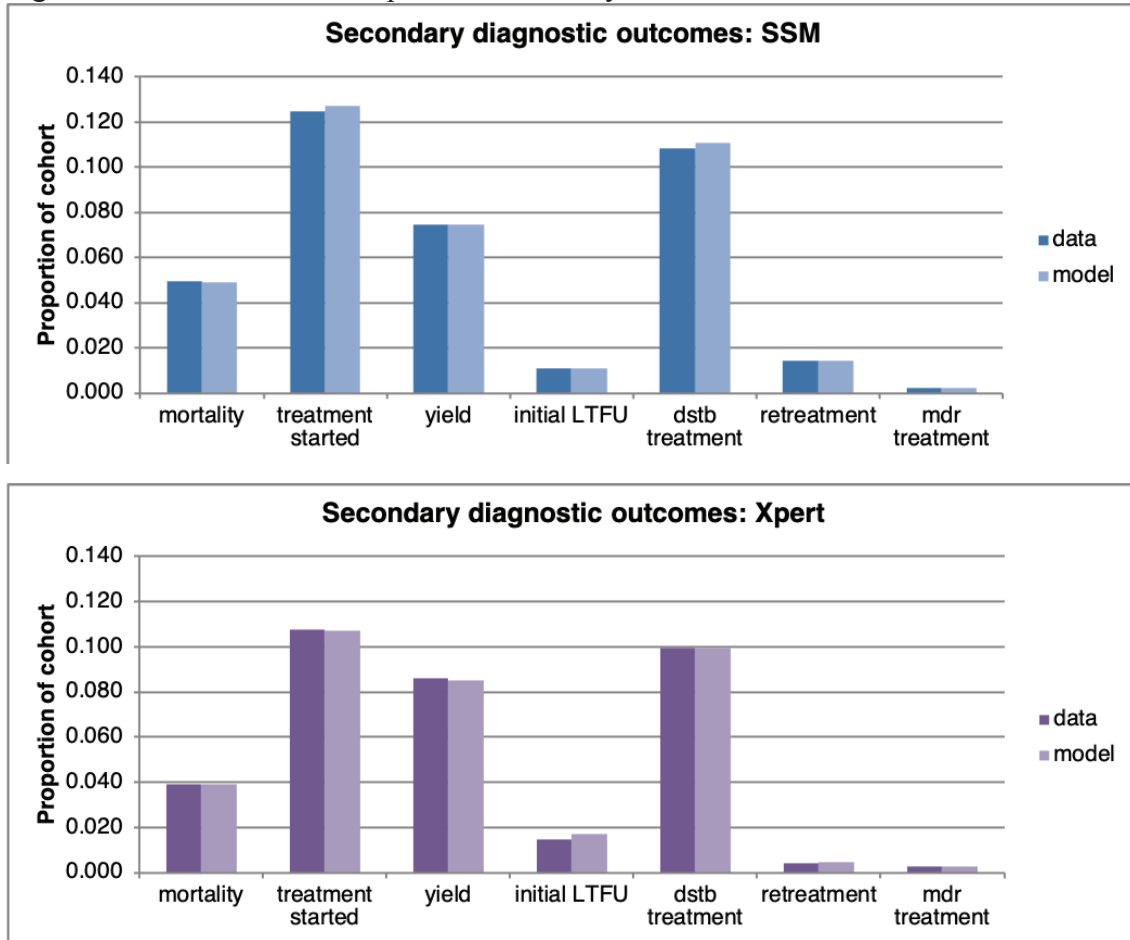
Model validation is crucially important given the size and complexity of many of the models used to make decisions for public policy. As models become larger and more complex with interacting mechanisms, debugging becomes complicated, even impossible. Validation processes and model reviews by a second technical expert therefore becomes an important step in building models that are producing results we can be confident in (264). The process may therefore be used to assess the validity of the

model for various purposes, these can be categorised as the technical -, predictive -, and face validity of models. I will discuss each of these in turn with an explanation for how this was assessed within the model.

The technical validity of the model relates to minimising and checking for programming, data entry errors or logical inconsistencies. These may be minimised by using a consultative process during model development, by using conceptual frameworks to explicitly show how interactions are conceptualised, through code or model reviews by a second technical expert or by repeating the process and building a second model to assess whether the results are similar. In this model, we used a theoretical framework to guide model development, a second technical expert reviewed the model and after the development of the initial model, I rebuilt the model several times and assessed the outputs against previous versions of the model to identify technical errors.

The predictive validity of the model refers to how accurately the model represents observed reality. Predictive validity of a model is tested by comparing intermediate and final outcomes with observed outcomes. In the development of this model, a strength of the model is the validation and calibration of the model outputs against the trial intermediate and final outcomes. This was done by firstly comparing the intermediate diagnostic outcomes of the model against the trial results (265). The outcomes compared included 1) mortality, 2) treatment started, 3) yield, 4) initial loss-to-follow-up, 5) number of patients starting DSTB treatment, 6) number of people starting retreatment, and 7) number of people starting MDR TB treatment. Other than helping to identify parameter values and improve the predictive value of the model, the iterative process of comparing the combined output across model inputs, assisted in understanding and exploring the relationships between input parameter estimates and how to represent this in the model structure (266). Figure 12 shows a comparison between the secondary diagnostic outcomes of the cohort, with the modelled outputs at the end of six months shown in light blue and purple respectively against the dark colours representing the data.

Figure 12: Assessment of the predictive validity of the initial models



Finally, the face validity of the model refers to the process of comparing our assumption of what should be happening with what actually happens in the model. The face validity of this model was assessed by comparing the model results against other published analyses to see whether the results are in line or where there are discrepancies, whether they can be explained by differences in modelling techniques. Secondly, the face validity of the model was tested by varying key model parameters and assessing whether the model outcomes responded as would be expected.

4.6.2 Model calibration

While model validation is the process of comparing the outcomes of the model to observations, calibration refers to the iterative process of varying the values of unobserved variables until the outcomes of a model fits the outcomes being fitted to (267). Cohort study data, where the same individuals are followed up and observed at multiple timepoints, is preferred as time-series calibration targets because it allows for

the control of birth cohort effects (267). A strength of this study is the use of detailed empirical data, which include transitions through care pathways and resource use, from a single cohort.

The challenge with calibrating decision analysis models relates to the fact that these models typically model micro-processes, where there is a need for greater precision when estimating the resource utilisation and resulting costs of an intervention (268,269). The trade-offs during calibration and validation is that if the values are fitted to many narrowly specified calibration ranges, the model may be overfitted and not be as representative of the system it is trying to emulate when extrapolating from the available data (230). Using measures to consider the overall fit of the curve as opposed to a fitting to a single point, mediates this challenge to some extent as places the focus on patterns of behaviour as opposed to a single statistic.

We calibrated the original model structure to both arms (smear microscopy as well as Xpert MTB/RIF) of the trial, in order to refine the structure and explore covariates that drive the differences between the study arms in more detail. During the analysis, the model is then restricted to the Xpert arm only, with supportive investments. An implicit assumption made in models that expresses the patient care cascade is that the difference between what is currently happening, and the ideal can all be attributed to the incorrect implementation of clinical guidelines. This modelling approach of expressing movement through the model doesn't explicitly express that health care worker behaviour and disease processes may be confounding variables in this relationship. In the model presented here, the interactions that influence healthcare worker decision-making is explicitly modelled, thus exploring interacting variables that drive behaviour.

Given the pragmatic nature of the trial whereby there was no interference with public facilities' current practice, the gold standard for TB diagnosis, culture was not artificially requested for each patient (culture for all was not part of the South African TB diagnostic guidelines at the time of the study). Therefore, given that neither smear microscopy nor Xpert is likely to identify every patient with TB, we were unable to empirically estimate what proportion of those with a negative diagnostic test result were correctly started on treatment i.e. the sensitivity and specificity of healthcare workers' intuitive judgement to start people on treatment without a definitive TB test result. The calibration was used to

estimate the best combination of values to allow for a good fit of the model to the empirical data. The unobservable parameters in the model included 1) the effectiveness of clinical decision-making to correctly start those with TB on treatment from a negative test result and 2) the effectiveness of clinical decision making in the diagnostic algorithm in starting those with TB correctly on treatment. We therefore calibrated, through a sequential, iterative process, the mortality curve generated from the model output, to the Kaplan-Meier mortality curve from the trial. In a similar process, we calibrated the time-to-treatment curve from the model output to the Kaplan-Meier time-to-treatment curves from the trial. The best fit was deemed the configuration of behaviour that provided the best fit of both the mortality and treatment curves simultaneously.

To derive this from trial observed mortality (up to six months after a diagnostic test) and measured health care worker behaviour and outcomes, we populated our model with mortality rates from secondary data, shown in Table 11. Figure 13 shows an example of how the 2x2 table was used to estimate the Positive – (PPV) and Negative Predictive Values (NPV) of the diagnostic processes.

The probability of bacteriologically confirmed TB from a positive or negative TB test result (the positive – or negative predictive value of the test) was estimated based on the reported sensitivity and specificity of the test, and the number of positive test samples in the trial (268,269). The approach is demonstrated below, using the example of Xpert MTB/RIF arm of the study. The same approach is then repeated to estimate the probability of TB if test positive $p(\text{TB}|\text{test positive})$ and the probability of TB if test negative $p(\text{TB}|\text{test negative})$.

For *Xpert MTB/RIF*, we used the pooled sensitivity 0,860 in those HIV negative and 0,790 in those HIV positive and those HIV positive on ART as estimated in the meta-analysis (269). A specificity of 0,99 was used.

	A	B	C	TB prevalence
HIV negative; sens 0,860 and spec 0,99				
		TB	nTB	
1	+	6.75	0.92	7.67
2	-	1.10	91.23	92.33
3		7.85	92.15	100
	P(TB test positive)	0.880		
	P(TB test negative)	0.012		
HIV positive; sens 0,790 and spec 0,99				
		TB	nTB	
4	+	9.55	0.87	10.43
5	-	2.54	87.03	89.57
6		12.09	87.91	100
	P(TB test positive)	0.916		
	P(TB test negative)	0.028		
HIV positive on ART; sens 0,790 and spec 0,99				
		TB	nTB	
7	+	4.51	0.94	5.45
8	-	1.20	93.3471	94.55
9		5.71	94.29	100
	P(TB test positive)	0.828		
	P(TB test negative)	0.013		
				9.89

Figure 13: Xpert unadjusted 2x2 table

A3 in Figure 13, TB prevalence, was estimated using the sensitivity and specificity of the test, solving for x in the following equation:

$$0.86x + 0.01(100-x) = 7.67$$

$$0.86x + 1 - 0.01x = 7.67$$

$$0.86x - 0.01x = 6.67$$

$$0.85x = 6.67$$

$$x = 7.85 \text{ which relates to cell A3}$$

A1 was then estimated by multiplying the sensitivity of the test by A3.

C1 was estimated by dividing the number of positive over the total sample (from the dataset).

$$\text{The } P(\text{TB}|\text{test positive}) = \text{TB+}/ \text{Allpos}$$

$$\text{The } P(\text{TB}|\text{test negative}) = \text{TB-}/ \text{Allneg}$$

For the *sputum smear microscopy* arm of the model, we used the pooled sensitivity of fluorescent microscopy calculated in a meta-analysis; 0,723 in those HIV negative and 0,446 in those HIV positive (270). In those HIV positive on ART, we used the same sensitivity as the general HIV positive value provided. A specificity of 0,999 was used. The TB prevalence in each of the samples, was unknown. TB prevalence was therefore estimated using the same approach as described above and estimated a prevalence of 13.19%.

Given that the population modelled was the microscopy arm of the trial, we re-estimated the probabilities of TB from test positive and test negative for a population with a TB prevalence of 13.19%. The revised probabilities were:

HIV negative

$$P(\text{TB}|\text{test positive}) = 0.877$$

$$P(\text{TB}|\text{test negative}) = 0.012$$

HIV positive

$$P(\text{TB}|\text{test positive}) = 0.936$$

$$P(\text{TB}|\text{test negative}) = 0.038$$

HIV positive on ART

$$P(\text{TB}|\text{test positive}) = 0.938$$

$$P(\text{TB}|\text{test negative}) = 0.039$$

From the probability of TB after the test result, we needed to estimate the probability that health care worker's decision-making after a negative test result was either correctly identifying TB or not. In other words, whether health care workers were correctly starting patients with TB on treatment after a negative test result, averting associated mortality and whether their decision to provide additional testing after a negative test result was correctly identifying TB or not. Starting TB treatment earlier, would reduce TB associated mortality if correctly started on treatment.

The initial distribution of the probability to start TB treatment after an initial negative test result was estimated using the following equation:

$$N_{i,t} = A_{i,t}R + B_{i,t}W \quad (2)$$

Where: N is the probability of a health care worker acting as if the patient has TB (either by ordering further diagnostic tests or by starting treatment based on clinical suspicion), after a negative test result, where further diagnostics are not ordered at time t and for individual type i ; A is the probability of true TB at time t and for individual type i with this decision being the correct decision i.e. true TB represented by the letter R; B is the probability that the patient does not have TB at time t and for individual type i with this diagnostic decision therefore being incorrect presented by the letter W.

We started the calibration, initially assuming that health care workers had an equal chance of correctly and incorrectly identifying someone as having TB, no difference between the decisions to start people on treatment from a negative test result and doing additional tests for the diagnostic negative pathway, the impact of the change in probability on the predicted mortality in the model was sequentially calculated and matched against the Kaplan-Meier mortality curve from the trial, see Figure 14 and Figure 15.

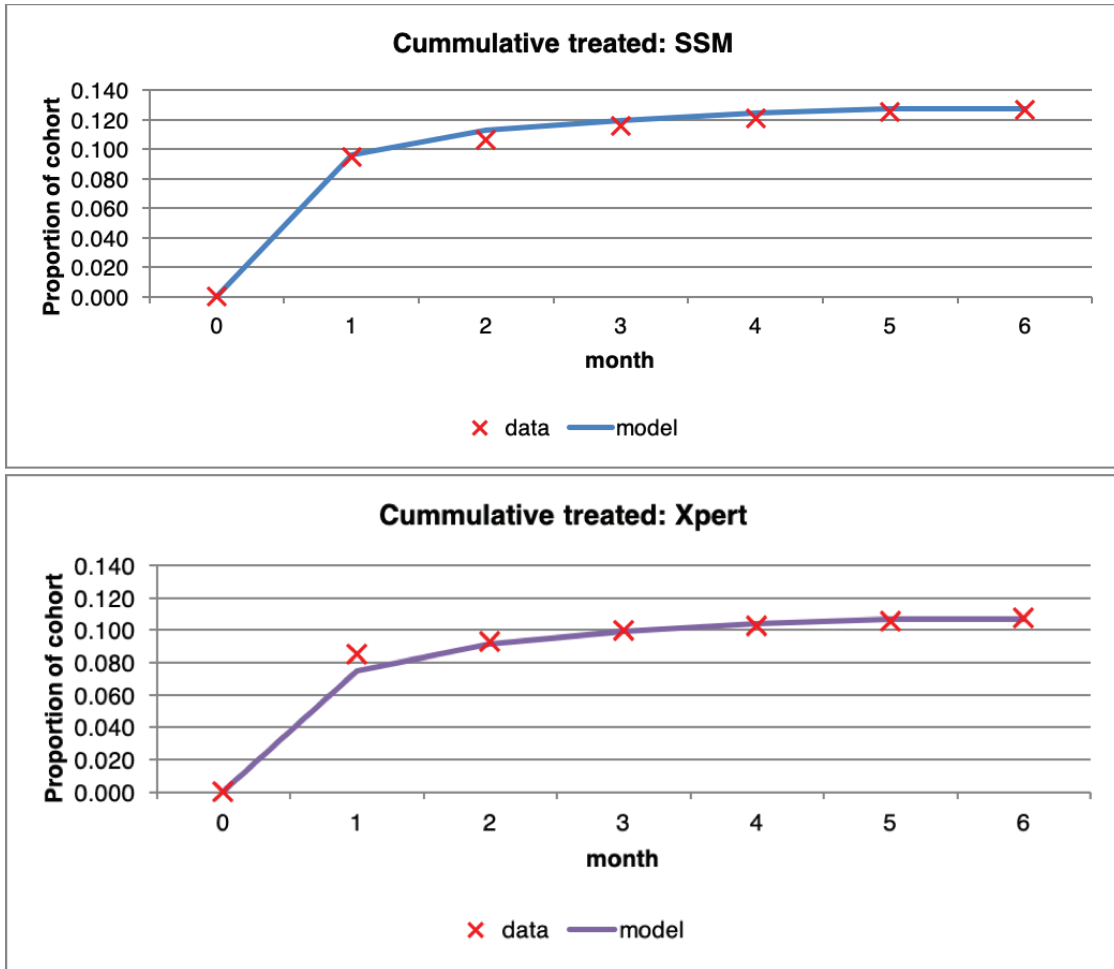


Figure 14. Comparing the fit of the time-to-treatment curves from the empirical data to the modelled estimates

The graph shows the cumulative proportion of the modelled cohort at monthly intervals. The model estimates of the time to starting treatment is represented by the solid line, with data points from the cohort study is presented as red crosses at each of the monthly time points. Two graphs were generated, one representing the sputum smear microscopy arm of the cohort; and the other the arm of the study that were randomised to receive a Xpert MTB/RIF test.

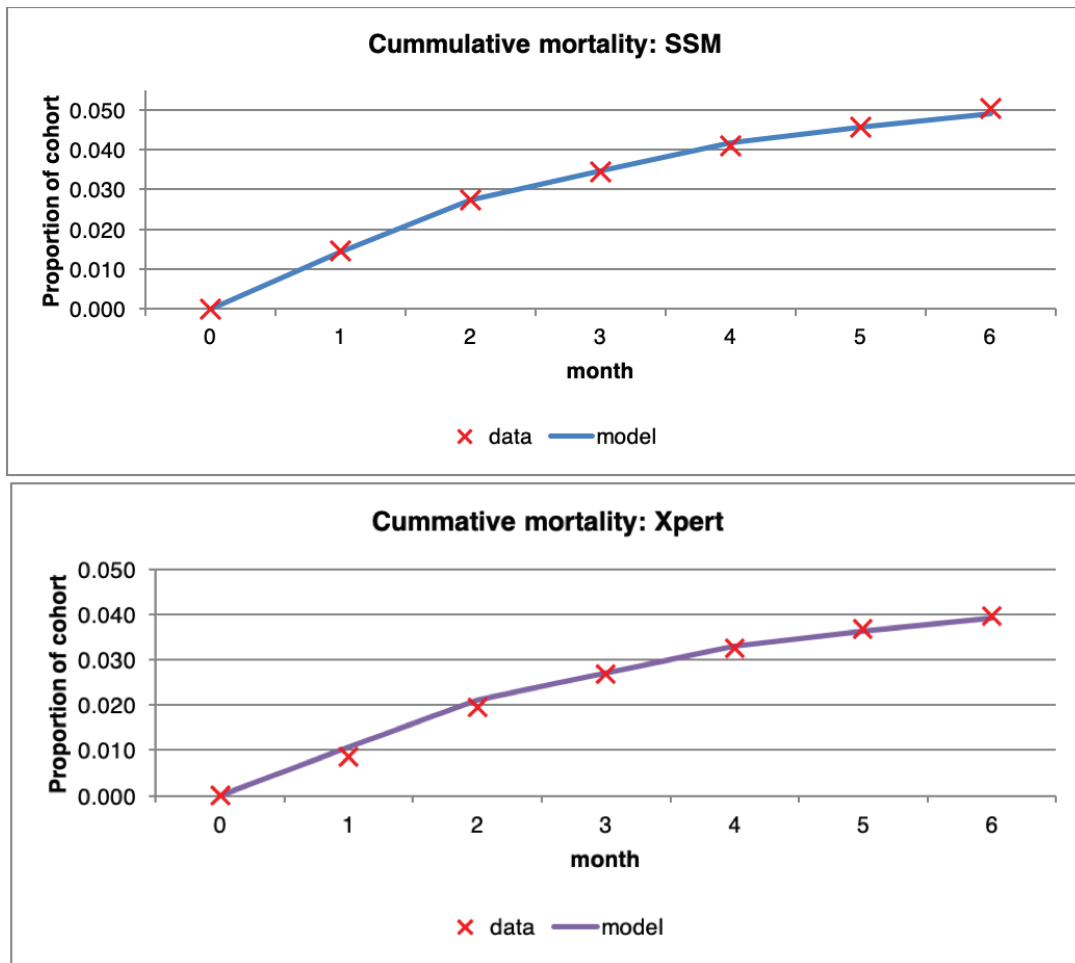


Figure 15. Comparing the fit of the time-to-death curves, model outputs to the data
 The graph shows the cumulative proportion of the modelled cohort at monthly intervals. The model estimates of the time to death is represented by the solid line, with data points from the cohort study is presented as red crosses at each of the monthly time points. Two graphs were generated, one representing the sputum smear microscopy arm of the cohort; and the other the arm of the study that were randomised to receive a Xpert MTB/RIF test.

The probability of starting treatment from a negative test result or from the negative pathway was estimated from the empirical data. Given the use of conditional probabilities to drive movement through the model, the calibration equations resulted in adjustments needed in other parts of the model, such as the denominator for treatment from out of care. These were calculated in a populated Excel spreadsheet. For each of the three uncertain parameters, we sequentially calibrated the probability to fit the mortality curve against the trial data observed in the trial, both in size and shape of the curve over time. With each subsequent calibration, the effect on related variables was re-estimated and repopulated in the appropriate model parameters.

Table 4. Measures of model fit.

	Smear microscopy						XPert MTB/RIF					
	ME_mort	ME_treat	SqE_mort	SqE_treat	points_mort (<5)	points_treat (<20)	ME_mort	ME_treat	SqE_mort	SqE_treat	points_mort (<5)	points_treat (<20)
RW1_EPTB0%	-42	-200	55	1143	6	6	8	158	5	694	6	0
RW1_EPTB2%	-5	-183	5	953	6	6	28	167	26	780	3	0
RW1_EPTB4%	16	-166	18	780	4	6	48	177	73	870	1	0
RW1_EPTB6%	37	-148	58	625	3	6	68	186	147	964	0	0
RW1_EPTB8%	58	-131	127	489	2	6	88	196	247	1064	0	0
RW0.5_EPTB0%	-23	-154	17	690	6	6	10	175	6	854	6	0
RW0.5_EPTB2%	-2	-140	5	569	6	6	31	179	31	893	3	0
RW0.5_EPTB4%	19	-127	23	461	4	6	52	183	84	933	0	0
RW0.5_EPTB6%	40	-113	69	365	2	6	73	187	167	973	0	0
RW0.5_EPTB8%	62	-99	146	281	2	6	93	191	277	1015	0	0
RW0.25_EPTB0%	-22	-131	16	506	6	6	11	184	7	941	6	0
RW0.25_EPTB2%	-1	-119	6	415	6	6	32	185	34	953	3	0
RW0.25_EPTB4%	21	-107	25	333	4	6	53	186	90	965	0	0
RW0.25_EPTB6%	42	-95	75	261	2	6	75	187	177	977	0	0
RW0.25_EPTB8%	64	-83	155	199	2	6	96	189	294	990	0	0

In the Table; each of the values represents the arithmetic mean drawn across 1 000 model samples. ME is the marginal error and SE represents the square root of the marginal error. The columns labelled points represents the number of points in the time-series where the model results are acceptably close to observations (within 5 or 20 units).

The difference between the curve and the trend line was determined by plotting the empirical data. The fit of the curve was expressed using three metrics; the maximum error (ME), the square root of the error (SqE) and the number of points in the time-series where the model results are acceptably close to observations (within 5 or 20 units).

ME_mort represents the maximum error which is the sum of the differences between model estimates of mortality and the value observed in the trial. The maximum error is to be minimised; ME_treat is a similar statistic but refers to the proportion of those in the cohort who start treatment; SqE_mort refers to the mean squared error or the difference between the observed and modelled estimates of mortality and treatment started (SqE_treat); points_mort and points_treat is a measure of the number of points modelled that are within in the first instance five units, followed by 20 units from the point observed from the trial. This measure therefore speaks to the fit of the trend. To find the best fit for the combined curves representing the relationships between treatment started and mortality reduction, the squared error of mortality was plotted against the squared error of treatment, summarised in Table 4, and shown graphically in Figure 16. The plot closest to the left and lowest on the y axis corresponds to the plot that represents the best fit of the interaction between mortality and TB treatment.

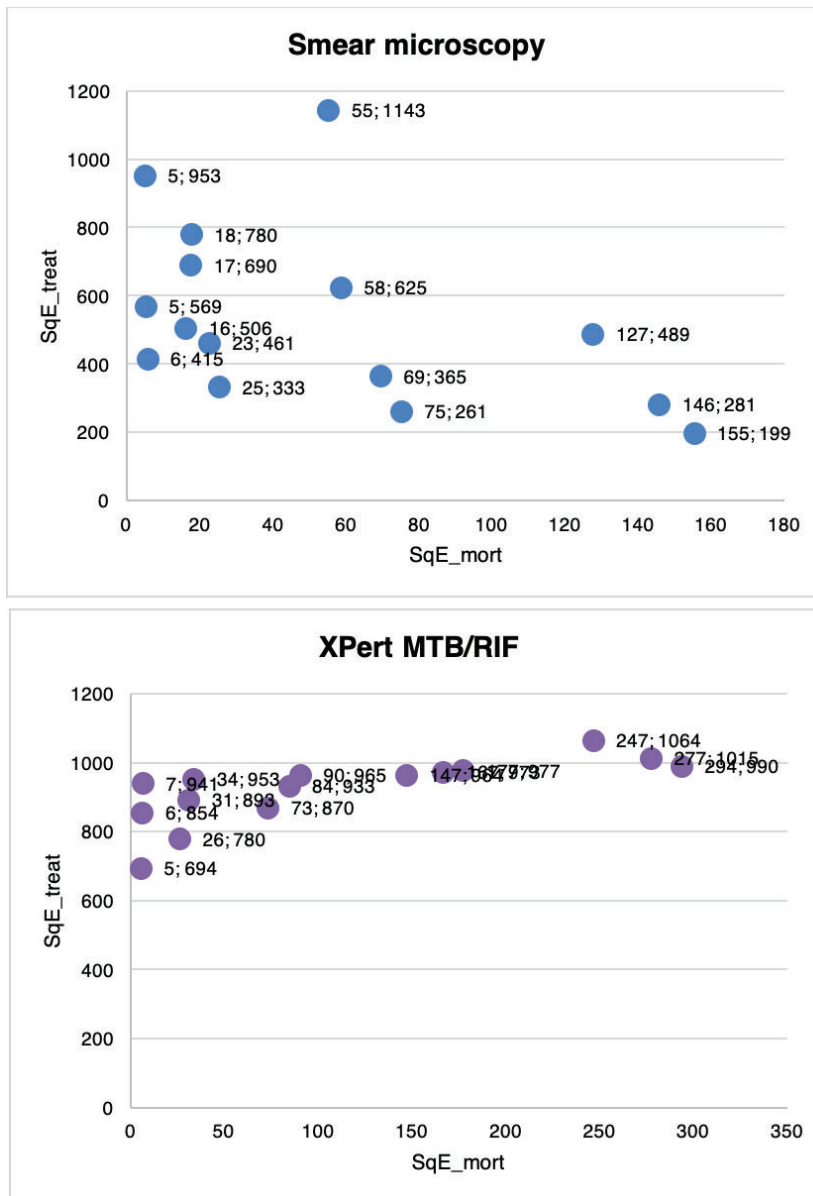


Figure 16. Degree of fit, identifying best fit of the graphs based on both mortality and TB treatment started. In the figure, SqE_treat represents the square root of the error (SqE) of the difference between observed and modelled representations of the time to treatment curve; and SqE_mort represents the square root of the error (SqE) of the difference between observed and modelled representation of the time to mortality curve.

In the control arm of the analysis, sputum microscopy, the best fit was at the point where health care workers had a 0.25 probability of making the correct decision; with a prevalence of extra-pulmonary TB of approximately 2%. In contrast, the fit of the Xpert arm of the trial estimated a 0% prevalence of extra-pulmonary TB and a probability of 1 of making the correct decision. This result is supported by other analyses of the trial data, that found that the Xpert arm of the trial was slightly healthier than the microscopy/control arm and that health care workers were more likely to conduct further diagnostic tests and start treatment empirically in the microscopy arm of the trial than in the control

arm (12,271,272). The unobserved transition probabilities estimated during the calibration and used in the analyses are summarised in Table 11.

The baseline characteristics of the cohort in the arms of the trial were slightly imbalanced as described above. The model was adjusted for the imbalance in patient population between the two arms of the trial, by implementing the following changes. The calibration modification to account for healthier patients in the smear arm of the trial:

- remove calibration modification (50% mortality reduction for those HIV positive) for healthier patients in the GX arm
- same proportion of HIV and ART types of individuals through the model
- recalculate (using the 2x2 tables) the probabilities of having a positive test result and starting treatment based on an equivalent bacteriologically confirmed TB prevalence between the two arms

4.7 Constructing comparators

The comparators and interacting mechanisms were identified from the empirical data analyses and these interactions are summarised in Table 12 and discussed in more detail in section 6.2.5.

4.8 Uncertainty and sensitivity analysis

The estimation of the decision uncertainty in an economic evaluation is an important part of the analysis. It is important to distinguish between variability, heterogeneity and decision uncertainty. Variability refers to differences that occur between patients by chance, it is the element of randomness and is sometimes referred to as first order uncertainty. Heterogeneity relates to the differences between patients that can be explained, these may include gender, and age. Uncertainty is the element that we are seeking to capture in our models; and can be further categorised as either parameter uncertainty (second order uncertainty) or structural uncertainty. Structural uncertainty

refers to the assumptions imposed by the modelling framework. We explore the impact of uncertainty on our estimates by conducting a range of sensitivity analyses (273: 61).

4.8.1 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) is used to jointly assess the uncertainty in all parameters and the implications for decision uncertainty. The results of the PSA are presented in Table 13 as uncertainty estimates.

4.8.2 Univariate sensitivity analyses

Univariate sensitivity analyses were conducted, whereby each individual variable in the model is varied downwards by a factor of 10, to provide a low estimate; and upwards by a factor of 10 to provide a high estimate of the outcomes of interest, namely provider costs, societal costs and disability adjusted life years (DALYs). The results of this analysis are shown in Table 15.

4.8.3 Multivariate sensitivity analysis

Univariate sensitivity analyses, while useful to identify individual drivers of our predicted estimates, have limited explanatory utility in identifying model assumptions that will alter the decision to choose one investment scenario over another. Multiple variables interact along a decision pathway to produce a cost or an effect, so for example, increasing the value of the unit cost of a chest x-ray is unlikely to be identified as a key driver of the results if a low proportion of the cohort is identified as needing additional diagnostic tests after an initial negative TB test result. These issues are correlated as healthcare workers' decisions to follow-up a patient after a negative TB test result will be influenced by the availability of chest x-ray facilities, a possible investment strategy. Complementary to the univariate sensitivity analyses, multivariate sensitivity analyses were used to further explore drivers of the investment decision, by varying a set of parameters simultaneously. The results of these analyses are shown in Table 14. Based on the results of the univariate

sensitivity analyses, as well as key variables identified during the model calibration, drivers of the decision were identified.

4.9 Strengths and limitations of the model

Modelling disease processes alongside patients' detailed movement through care, needs careful consideration for the structure of the model, as these diagnostic models rapidly become very inflexible. In this model, I wanted to maximise the use of the detailed data available, while still being able to have enough flexibility to explore the behaviour of healthcare workers.

The additional value of this model-based analysis however rests on extensive primary cohort data collected, the rigour of the evaluation of the trial cohort, as well as the range of perspectives, both provider and patient included in this analysis. However, given the very detailed micro-processes modelled, the model is less flexible when estimating uncertainty intervals around the main estimates.

4.10 Conclusion

This chapter provides an overview of the methods used in developing and parameterising the model. The structure of the model was developed based on an initial conceptual framework of the mechanisms (disease and process) that influence the progression of patients to the outcomes observed. The model parametrisation was based on the data generated as part of a pragmatic cluster randomised control trial. However, the trial was not able to collect data to estimate the TB prevalence in the cohort. The parameterised model was therefore validated against the process outcomes from the trial and calibrated to estimate the prevalence of TB in the cohort. From there, and based on a literature review, plausible health system investments to support TB diagnosis were constructed. Uncertainty in the results was explored by varying individual parameters in the univariate sensitivity analysis, followed by multivariate sensitivity analysis to better understand the effect that the interaction of changes in multiple parameters may have on the decision recommendation.

CHAPTER 5: ECONOMIC BURDEN OF TUBERCULOSIS

Summary

This chapter discusses the analysis, specific methods and results of the longitudinal patient cost study. These results were also used in Chapter 6 to estimate the societal perspective of the cost-effectiveness results. Social protection against the cost of illness is a central policy objective of Universal Health Coverage and the post-2015 Global strategy for Tuberculosis (TB). Understanding the economic burden associated with TB illness and care is key to identifying appropriate interventions towards achieving this target. The aims of this study were to identify points in patient pathways from start of TB symptoms to treatment completion where interventions could be targeted to reduce the economic impact on patients and households, and to identify those most vulnerable to these costs. Two cohorts of patients accessing TB services from ten clinics in four provinces in South Africa were surveyed between July 2012 and June 2013. One cohort of 351 people with suspected TB were interviewed at the point of receiving a TB diagnostic and followed up six months later. Another cohort of 168 patients on TB treatment, at the same ten facilities, was interviewed at two-months and five-months on treatment. Patients were asked about their health-seeking behaviour, associated costs, income loss, and coping strategies used. Patients incurred the greatest share of TB episode costs (41%) prior to starting treatment, with the largest portion of these costs being due to income loss. Poorer patients incurred higher direct costs during treatment than those who were less poor but only 5% of those interviewed were accessing cash-transfers during treatment. Indirect costs accounted for 52% of total episode cost. Despite free TB diagnosis and care in South Africa, patients incur substantial direct and indirect costs particularly prior to starting treatment. The poorest group of patients was incurring higher costs, with fewer resources to pay for it. Both the direct and indirect cost of illness should be considered when setting levels of financial protection and social support, to prevent TB illness from pushing the poor further into poverty.

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5.1 Introduction

Social protection against the cost of illness is a central policy objective of Universal Health Coverage and correspondingly the post-2015 Global strategy for Tuberculosis (TB) (274). Social protection strategies include access to health care, financial protection against the cost of seeking care and poverty alleviation strategies (275). The post-2015 strategy aims for ‘no affected families facing catastrophic costs due to TB’ by 2025. Reducing the impact of the cost of illness is of concern in TB control, due to the synergy between poverty and TB disease. Poverty has been linked to a greater risk of infection, poorer patient outcomes as well as affecting health-seeking behaviour (49,276–279). In addition, TB disease also worsens poverty by reducing patients’ physical strength and ability to work, ultimately leading to loss of income (193,200). The economic impact on the household is then further exacerbated by the costs incurred while seeking health care (52). In South Africa, the economic burden of ill health on households could potentially be severe, given that 30% of the global incident cases of TB-HIV co-infection occur in South Africa, which roughly equates to 530 000 people being infected with TB per annum (280,281).

Historically, studies seeking to quantify the financial burden of TB on patients have focused on the out of pocket costs measured at a single point in time, with questions asked about retrospective expenditures. This approach suffers from several limitations, in that the measurement of cost is often not comprehensive, the economic impact on patient’s social networks is not captured, and there is little insight provided on how patients adapt over time (195). The costs typically measured, referred to as direct costs, include transport costs to and from the health facility and any costs for medication or consultation incurred by individuals while seeking care. The magnitude of these direct costs is then compared against the annual household income, individual income or the household’s expenditure on food (216). Various thresholds for quantifying the level of direct cost that is likely to drive households into poverty have been used, including 10% or 15% of annual household or individual income, and 40% of household non-food expenditure (212,282–284). Using these measures, previous TB costing studies have found that direct costs can be ‘catastrophic’ for many households and have called for further research to

identify households that are particularly at risk of catastrophic expenditures (195,197,199,285).

There is greater paucity in terms of the measurement of costs associated with the time lost while being unable to work due to seeking care or being too ill to work. These so-called indirect costs are used to capture the productivity and economic costs an individual or household incurs because of being ill or spending time seeking treatment (77,195,286). There are several methods to value time loss. The most common method is the Human Capital Approach, which considers a set of marketable skills of workers as a form of capital that is then used to produce an output, income for the worker, and a contribution to the economy for society (205,287). Following this approach, an individual's time (or loss of productive time from treatment and illness) is valued based on their productive output, in the form of their reported income prior to being ill. This has equity implications given that it excludes the value of time loss of those not employed or looking after family at home. Alternative approaches include the equality of wages method where time loss is valued equally across individuals by using a proxy such as the minimum wage or the average reported income for the cohort (199,209). However, simply attaching a value of time lost may not provide sufficient insight into changes in income over time, particularly the ability to recover income following a period of illness; and they may not capture the broader impact to the household, nor the ability of society to compensate any social welfare lost (206).

Russell et al. made an important contribution to the understanding of costs of illness from a household perspective by highlighting the importance of and expanding the definition of households' 'ability to pay' for health care to include the mobilization of additional resources including borrowing from family members, selling assets, forgoing consumption on other essential commodities, or delaying payment (214). Longitudinal household surveys suggest a heterogeneous economic impact of health costs on households, with some households demonstrating a resilience to high out of pocket costs while others are forced into poverty by relatively small expenditures (196). In South Africa, a longitudinal household study found that household resilience against catastrophic costs was dependent on social support structures within communities, such as being able to borrow money without interest, and someone to take over jobs or household tasks or to care for an individual who is ill. Household resilience was found to

diminish as chronic illnesses, such as HIV, increased the economic loss over time and jeopardised the long-term welfare of the family (200).

In South Africa, there are a limited number of studies that have estimated the patient costs associated with TB care. Previous studies found that direct costs and time spent accessing health care could be substantial and that the cost of TB care varies between socio-economic groups (209,288,289). However, these studies suffer from many of the weaknesses highlighted above. They did not include the patient costs prior to starting treatment or examine in-depth how costs and income changed over time.

We present a longitudinal study of the economic burden on individuals and their social networks, from the start of TB symptoms to the end of treatment in South Africa. Indirect costs are estimated using reported income loss and costs are presented by socio-economic status (SES), to explore how the economic burden on patients and their social networks evolves as patients negotiate their way through the healthcare system during TB illness.

5.2 Methods

5.2.1 Analytical framework

Economic burden (Figure 1) was conceptualised by drawing on the Access framework proposed by McIntyre et al. (2009) to examine the interactions between individuals and the health system that are likely to impact on patients' health seeking behaviour (290). In terms of exploring the consequences of these interactions, in addition to estimating the out-of-pocket costs incurred by individuals, we examined reliance on social networks to mediate a catastrophic financial impact on the household (286).

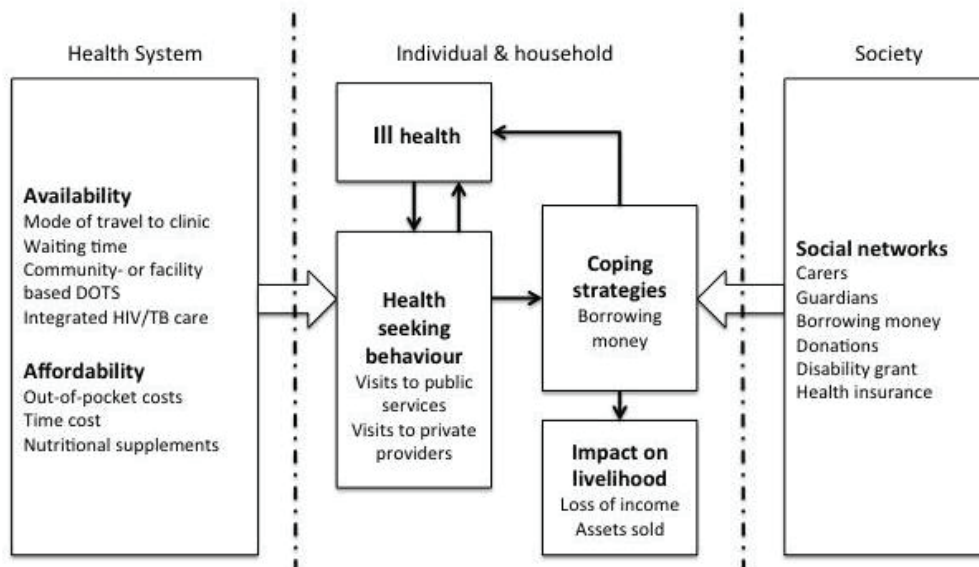


Figure 17. Dimensions of economic burden on individuals and households and interactions with the health system, adapted from Russell (2004) and McIntyre (2009).

Social networks were defined to include people from an individual’s community who can take over job-related or household related tasks while the individual is ill (‘carers’); to accompany the patient to the clinic (‘guardians’); and being able to borrow money without paying interest or receiving donations. The availability of cash transfers and health insurance was also conceptualised as a component of the patient’s social network, which could potentially alleviate some of the catastrophic consequences of ill health.

5.2.2 Study design

To capture the economic impact of TB over time, and minimise recall bias, a prospective cohort study of patient costs was conducted as part of a cluster randomised pragmatic trial evaluating the implementation of Xpert MTB/RIF in South Africa, the ‘XTEND’ trial. Interviews were conducted between July 2012 and June 2013. Conducting a patient cost study as part of a trial offers the advantage of having sufficient infrastructure to follow patients up over time but can restrict sampling approaches. Figure 18 provides a timeline of patients’ trajectory through care seeking and treatment, the interview time points and periods used in the analysis. These time points were selected to co-ordinate with the main interview points in the broader trial. As the trial was pragmatic, the aim

was to not influence the patient pathway to capture ‘real world’ conditions and thus the frequency of interview was constrained.

The trial enrolled patients with symptoms suggestive of TB, who were then followed up six months later to determine patient outcomes (Figure 20 and Figure 21). Only 10% of those screened were projected to have TB. To capture the pre-treatment costs, we sampled from those with symptoms (cohort 1). However, it was not possible to capture sufficient numbers of those with TB, given that enrolment was conducted prior to the knowledge of whether a patient had TB, and due to the expense of conducting a full questionnaire on high numbers of trial participants. We therefore added a further cohort of TB patients who were recruited from the same clinics for the economic study alone (cohort 2), to fully capture the costs of those who proceed to TB treatment.

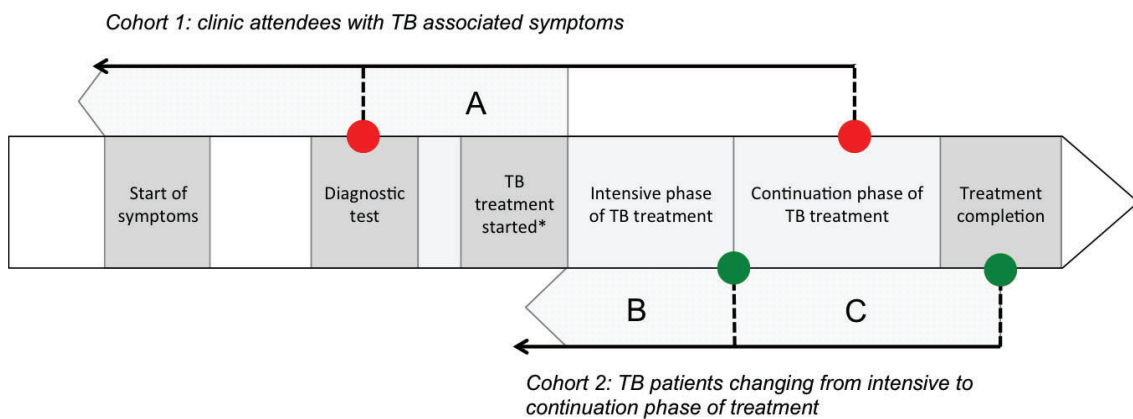


Figure 18. Timeline positioning data collection and time periods (A, B, and C) for patient cost analysis.

In the cohort of those enrolled in the main trial (cohort 1), every third trial participant enrolled at the sample sites was asked additional questions regarding their health service use, the associated costs experienced, as well as change in income from the start of TB symptoms. Patients were eligible if they were older than 18 years of age, would be living in the area for the next eight months, and were not currently on TB treatment. At the six-month follow up, respondents were asked about their health service use and the associated costs from the baseline visit to when they started TB treatment or until the end of their TB associated symptoms Figure 18. In cohort 2, TB patients were eligible if they were older than 18 years, had not been interviewed for the TB suspect cohort and had started treatment approximately two months previously. At the TB patient’s enrolment interview, respondents were asked to report on their health service use and the associated costs in

the last two months. They were followed up three months later and were asked about costs incurred in the last month.

5.2.3 Data collection

Ten public health clinics, in Gauteng, Mpumalanga, Eastern Cape and Free State provinces were purposefully selected from the trial sites to generate a representative sample of rural and urban sites, facilities with different workloads, plus the location of the clinics relative to the communities served. Clinic characteristics are described in the supplementary results section, Table 2. Data were captured using Epidata v3.1 and exported to STATA13 for analysis (291,292). To minimise recall bias, respondents were asked about the costs incurred during their last visit; per period costs were then calculated by multiplying the cost per visit against the number of visits reported during that period. Individual income was estimated by asking detailed questions about income categories, including formal employment, working from home, non-monetary payments, government grants, pension as well as infrequent or ‘piece’ work. Income from government grants and charity donations was also explicitly unpacked. Furthermore, to assist respondents in recalling what happened to them between enrolment into the study and starting treatment, interviewers used a timeline and anchored the questions to memorable events such as starting treatment.

5.2.4 Data analysis

Costs incurred were analysed for three time periods shown in Figure 18, from the start of TB-associated symptoms to the initiation of TB treatment for those who did start treatment (A) or until the amelioration of symptoms for those who did not start treatment. Followed by, for TB patients, the time from the start of treatment to the end of the intensive phase at two months (B), followed by the time during continuation phase of treatment (C). The dataset for analysis was restricted to respondents where a follow up interview was conducted and responses from patients who passed away or were lost to follow up were not included. In addition, those who were symptomatic but did not start TB treatment were analysed separately and are presented in the results as a comparison.

For each of the time periods described in Figure 18, the direct and indirect costs incurred by people with suspected TB and those on treatment were calculated. Direct costs were calculated by adding the cost of travel to and from facilities, admission or consultation costs, the cost of medication and/or food while admitted, and any fees paid in lieu of diagnostic procedures. In each period the overall cost was calculated by multiplying the number of visits by the cost per visit for the period. Indirect costs were calculated based on the reported income loss due to TB symptoms and/ or treatment. Finally, to explore the broader impact of the individual's illness on the economic costs' households faced, social resources were assessed by estimating the costs to adults accompanying the respondent to the clinic, time spent caring for or taking over the tasks of the individual who is ill, as well as money borrowed to cover costs (199,214). The opportunity costs of these 'carers' and 'guardians' were calculated by multiplying time spent by the average income of respondents prior to the start of symptoms.

Due to the uneven distribution of costs with a minority of respondents reporting high costs, mean and median values were reported for all cost estimates as measures of central tendency and standard deviation (SD) and inter-quartile ranges (IQR) were reported (293). To assess differences in costs between groups, p-values were calculated using non-parametric methods, two-sample Wilcoxon rank-sum test and the Kruskal-Wallis test. Logistic regressions were run to identify patient and health service drivers of both income loss (1 = yes; 0 = no), and 'catastrophic' costs (1 = more than 10% of annual individual income; 0 = no). Costs were converted to United States Dollars (US\$) using the 2013 average annual exchange rate of US\$1 = R9.62. (www.Oanda.com).

As a measure of individuals' ability to pay for out-of-pocket expenses, we compared direct costs incurred against annual individual income and defined costs as catastrophic if they exceeded 10% of individual income (284). Where individuals were earning no income, we performed a separate analysis, imputing an annual income of US\$1 when calculating catastrophic costs. This approach was presented separately to highlight the burden on households with no incomes (216). A range of household measures of SES were collected, and an asset index was created using Multiple Correspondence Analysis (MCA). Variables used to create the asset index included type of house, material of walls, floors, type of water supply and toilet, possession of a bicycle or a car, as well as other assets such as an electric stove, radio, and livestock. MCA as opposed to Principal

Components Analysis (PCA) was used to create the asset index as MCA makes fewer assumptions about the underlying distributions of indicator variables and is more suited for the analysis of categorical variables (294–296).

5.2.5 Ethics

The human research ethics committees at the University of Cape Town (363/2011), University of the Witwatersrand (M110827), London School of Hygiene and Tropical Medicine (6041), and the World Health Organisation (RPC462) granted ethical approval for the study. Health department officials and facility managers provided permission to conduct the study in the selected facilities and written informed consent was obtained from respondents.

5.3 Results

A total of 618 respondents were interviewed. In the first cohort, 385 respondents were enrolled, 23 died prior to the follow up interview and 11 were lost to follow-up (LTFU). Of the 351 respondents remaining, 37 had a positive diagnostic test and a total of 45 were started on first line TB treatment, three on retreatment and one on MDR TB treatment. In the TB patient cohort, 233 TB patients were enrolled at the two-month change of treatment phase, 5 died and 53 were LTFU. Direct costs incurred at enrolment were not significantly different between those retained in the study and those not ($p = 0.605$; $p = 0.269$).

5.3.1 Sample and setting characteristics

Of those interviewed, 45% were in rural and 55% in urban settings. Within study clinics, a mix of facility based – and self-observed TB treatment was provided with varying levels of community-based support Table 2. Table 5 presents the respondent characteristics.

Table 5. Socio-demographic and clinical characteristics of respondents in the suspects and TB patient cohorts.

	Suspects n=351	TB patients n=175
Gender (% female)*	203 (58%)	78 (45%)
Mean age in years (median)	38 (36)	40 (39)
Self-reported HIV status (%)		
HIV negative	88 (25%)	30 (17%)
HIV positive on ART	52 (15%)	79 (45%)
HIV positive	154 (44%)	33 (19%)
Unwilling to share status	57 (16%)	33 (19%)
Educational status [§] (%)		
No formal education	256 (73%)	120 (69%)
School leavers' certificate	81 (23%)	49 (28%)
Tertiary education	13 (4%)	1 (0.6%)
Reported primary source of income ^{***} (%)		
Formal employment	86 (25%)	40 (23%)
Odd jobs	52 (15%)	23 (13%)
Self-employed	20 (6%)	9 (5%)
Maintenance	4 (2%)	1 (0.6%)
Pensioner	15 (4%)	5 (3%)
Government grant	41 (12%)	37 (21%)
Student	12 (3%)	3 (2%)
No income	121 (34%)	55 (31%)

In the table, § no formal education defined as all respondents without a high school leavers certificate; * 2 non-responses in the TB patients cohort; ** 1 non-response in the possible TB cohort and 5 in the TB patients' cohort; *** 2 non responses in the TB patients cohort.

The level of education in the sample population was lower than the general South African population, with 4% of respondents with post school education, compared to 12%. Similarly, the unemployment rate at 47% and 54% respectively was higher than the overall South African unemployment rate of 30% (297). Of the respondents, 12% and 21% respectively listed government grants as their primary source of income, while 21% and 18% respectively relied on odd jobs or self-employment as their primary source of

income. Only 34% and 38% of respondents indicated that other household members had a steady job. Levels of private health insurance were low in both cohorts (1% and 4%). When compared against the national statistics, these findings suggest that the respondents were particularly poor relative to the average South African household (297).

5.3.2 Costs associated with health service use

During the symptomatic period, the median time from experiencing symptoms to getting a TB test was 21 days, and in those who started treatment, the median time from test to treatment was one day. There was a statistically significant difference in the time with symptoms between poor and less poor patients ($p < 0.05$). In those who started treatment, the mean time from first symptom to TB test was 90 days in the poorest group compared to 33 days in the less poor group. Respondents' first port of call when experiencing symptoms was their local public clinic (80%) and patients made a mean of two visits to the public clinic. During the two-month intensive phase of treatment, a mean number of 12 (and a median of four) visits were made followed by 12 (and a median of eight) during the four-month continuation phase of treatment. Patients were collecting TB medication weekly or even monthly as opposed to daily Directly Observed Treatment (DOTS). Just under half of those in the TB patient cohort (45%) were HIV positive and on Anti-Retroviral Therapy (ART) but only 24% of those on ART could collect their TB medication and ART during the same clinic visit. Reported utilisation of traditional health care workers was very low (1%).

In Table 6, the direct costs incurred are presented and compared to respondents' annual individual income. This is followed by direct, indirect and total societal costs in Table 7. The mean total direct costs incurred by respondents in accessing health care during TB diagnosis and treatment were US\$111.83 or 12% of annual individual pre-symptom income and 53% of the total episode patient cost. The largest share of the direct costs was incurred during the pre-diagnosis and diagnosis phase. Direct costs were likely low given that TB care is provided free at primary health care clinics in South Africa and many respondents (61% and 66% respectively) could walk to the clinic to access care. Of the total direct costs, nutritional supplements - especially during the pre-diagnostic and diagnosis phase - were a substantial cost, with respondents spending an average of US\$12.54 during the symptomatic period. People Living With HIV and AIDS (PLWHA)

spent significantly more on supplements (US\$9.37) than those who were HIV negative (US\$5.35) ($p < 0.05$) which may reflect the emphasis placed on healthy diets during HIV/TB counselling. The costs associated with someone accompanying the respondent to the health facility (guardian costs) were greatest during the intensive phase of treatment. Similarly, the cost of someone to either take over the respondent's tasks or to look after them was greatest during the intensive and continuation phases of treatment.

Table 6. Pre-treatment and treatment direct costs (2013 US\$).

Period	Sample size	Non-transport direct costs		Direct transport costs		Time loss (hours), mean	Cost of nutritional supplements		Total direct costs, mean	Monthly income, mean*	Percentage of annual income**
		Mean	Median	Mean	Median		Mean	Median			
Pre-diagnosis & diagnostic	49	22.73	0.00	10.55	0.00	9	12.54	0.00	45.82	76.05	5%
Treatment (intensive)	175	29.80	0.00	4.33	0.00	59	1.10	0.00	35.23	76.05	4%
Treatment (continuation)	175	17.96	0.00	11.58	0.00	31	1.24	0.00	30.78	76.05	3%
Total episode cost		70.49	0.00	26.46	0.00	99	14.88	0.00	111.83	76.05	12%
No TB	302	17.63	0.00	6.04	0.00	14	6.26	0.00	29.93	107.51	2%

In the table, * Mean monthly individual income prior to the start of TB-associated symptoms; ** Percentage of mean annual individual income prior to the start of TB-associated symptoms.

Table 7. Pre-treatment and treatment indirect and total costs (2013 US\$).

Period	Sample size	Total direct costs, mean	Loan interest, mean	Reported income loss		Total cost to the patient, mean	Percentage of annual income	Guardian costs, mean	Carer costs, mean	Total cost, mean
				Mean	Median					
Pre-diagnosis & diagnostic	49	45.82	0.64	39.26	0.00	85.72	9%	7.46	1.94	95.12
Treatment (intensive)	175	35.23	6.57	15.56	0.00	57.36	6%	22.99	39.10	119.45
Treatment (continuation)	175	30.78	36.11	0.00	0.00	66.89	7%	1.66	40.95	109.50
Total episode cost		111.83	43.32	54.82	0.00	209.97	22%	32.11	81.99	324.07
No TB	302	29.93	0.34	62.13	0.00	92.40	7%	5.49	1.93	99.82

If we explore the costs incurred by SES, we find that the least poor group were spending a greater percentage of their annual income than those in the poorer group during the pre-diagnostic period. This can be explained by more visits to private health care facilities Table 8.

Table 8. Costs incurred (2013 US\$), presented by socio-economic status (SES) and over time.

	<i>Poorest[§]</i>		<i>Least poor[§]</i>		p-value
	mean	median	mean	median	
Pre-diagnosis & diagnostic period in those who start TB treatment: represents a mean of 45 days (n = 49)					
Public health facility visits, number of	3	3	3	3	0.845
Private health facility visits, number of	0	0	1	0	< 0.05
Total direct costs	24.35	0.00	55.57	17.36	0.173
Direct costs as % of annual individual income	1%	0%	6%	1%	0.346
Adjusted costs as % of income*	1000%	0%	3323%	2%	0.137
Time loss, number of hours	5	2	11	2	0.236
Reported income loss	50.86	0.00	67.25	0.00	0.539
Guardian costs	0.00	0.00	11.07	0.00	< 0.05
Carer costs	1.46	0.00	2.15	0.00	0.620
Total costs	76.67	38.61	136.04	66.73	0.501
Intensive treatment phase: represents a two-month period (n = 175)					
Public health facility visits, number of	15	4	11	4	0.885
Private health facility visits, number of	0	0	0	0	0.515
Total direct costs	52.88	0.00	17.11	0.00	< 0.05
Direct costs as % of annual individual income	3%	0%	3%	0%	0.812
Adjusted costs as % of income*	1514%	0%	285%	0%	< 0.05
Time loss, number of hours	62	21	44	15	0.412
Reported income loss	12.17	0.00	19.00	0.00	0.995
Guardian costs	17.35	0.00	18.97	0.00	0.609
Carer costs	18.14	0.00	32.67	0.00	0.362
Total costs	100.54	11.66	87.75	0.00	0.059
Continuation treatment phase: represents a four-month period (n = 175)					
Public health facility visits, number of	14	8	14	8	0.222
Private health facility visits, number of	0	0	0	0	0.196
Total direct costs	48.18	0.00	13.18	0.00	< 0.05
Direct costs as % of annual individual income	3%	0%	3%	0%	0.859
Adjusted costs as % of income*	3791%	0%	1183%	0%	< 0.05
Time loss, number of hours	35	14	25	12	0.332
Reported income loss	0.00	0.00	0.00	0.00	0.315
Guardian costs	3.08	0.00	0.22	0.00	0.405
Carer costs	1.98	0.00	5.38	0.00	0.627
Total costs	53.23	0.00	17.58	0.00	< 0.05
Total episode costs	230.44	50.27	241.37	66.73	
No TB (n = 302)					
Public health facility visits, number of	3	2	3	2	0.089
Private health facility visits, number of	1	0	1	0	0.096
Total direct costs	26.53	0.00	33.50	0.00	0.296
Direct costs as % of annual individual income	878%	0%	1800%	0%	0.168
Adjusted costs as % of income*	1%	0%	4%	0%	0.418
Time loss, number of hours	14	2	15	1	0.281
Reported income loss	82.00	0.00	109.80	0.00	0.849
Guardian costs	7.69	0.00	2.86	0.00	0.894
Carer costs	2.25	0.00	1.52	0.00	0.973
Total costs	118.47	25.85	147.68	16.00	0.788

In the Table, standard errors are not reported here due to space considerations; [§]The poorest group is represented in the lowest asset index tertile, and the least poor group is represented in the upper tertile; *In the adjustment for those with no income, we assumed an annual income of US\$1 in all with no income.

Once patients start TB treatment, we found that poor patients were spending a greater percentage of their annual income on costs associated with seeking care than those who

are less poor. The poorest group of patients were incurring higher direct costs, with fewer resources to pay for it.

5.3.3 Income loss

The mean monthly individual income of the entire cohort prior to starting symptoms was US\$103.12. Income prior to symptoms was considerably different between those who started TB treatment compared to those who did not, US\$76.05 and US\$107.51 respectively. Prior to symptoms, 59% of individuals in the cohort reported no income; this proportion was higher in the group that started TB treatment (69%).

Table 9. Logistic regression exploring drivers of income loss while symptomatic (n = 351).

Income loss (1 = Yes)	OR (95% CI)*	p-value
Gender (1 = male)	0.66 (0.35; 1.24)	0.196
Years of education	1.03 (0.93; 1.14)	0.609
HIV status	0.88 (0.57; 1.36)	0.566
Bacteriologically confirmed TB (1 = positive)	0.31 (0.10; 0.92)	< 0.05
Rural (1 = rural)	4.52 (2.18; 9.39)	< 0.05
Main income source = formal employment	reference	
Main income source = self employed	1.34 (0.42; 4.27)	0.616
Main income source = odd jobs	0.73 (0.32; 1.67)	0.462
Main income source = non-productive income	0.02 (0.01; 0.06)	< 0.05
Main income source = no income	0.03 (0.01; 0.07)	< 0.05
Days symptomatic	1.00 (0.99; 1.00)	0.059
Other HH member steady job	0.80 (0.39; 1.61)	0.525
Asset index (1 = least poor)	0.80 (0.56; 1.13)	0.202
Number of health care visits	1.07 (0.99; 1.15)	0.106
Pseudo R2 = 3948		

In the table, *OR = odds ratio; 95% CI = 95 percent confidence interval.

Income loss was significantly higher in those who didn't start TB treatment ($p < 0.05$) - but probably points to the higher percentage of those with no income (and hence no possible income loss) in the group that starts TB treatment Table 9. In addition, income loss was higher in rural communities and there was some protective effect in those receiving non-productive income such as government grants. The greatest share of income loss occurred in the period between the start of symptoms and starting TB treatment. During the intensive phase of treatment, there is a further net loss of income that is possibly tempered due to an income gain experienced by some individuals. During

the continuation phase, we see a small net loss that does suggest that individuals who had the initial loss of income may not regain income as quickly as we might have expected.

5.3.4 Coping costs and impact on social networks

In trying to understand the broader impact of ill health, direct costs and income loss, we explored the impact on social networks. The percentage of patients who employ coping strategies and access social resources are shown in Figure 19.

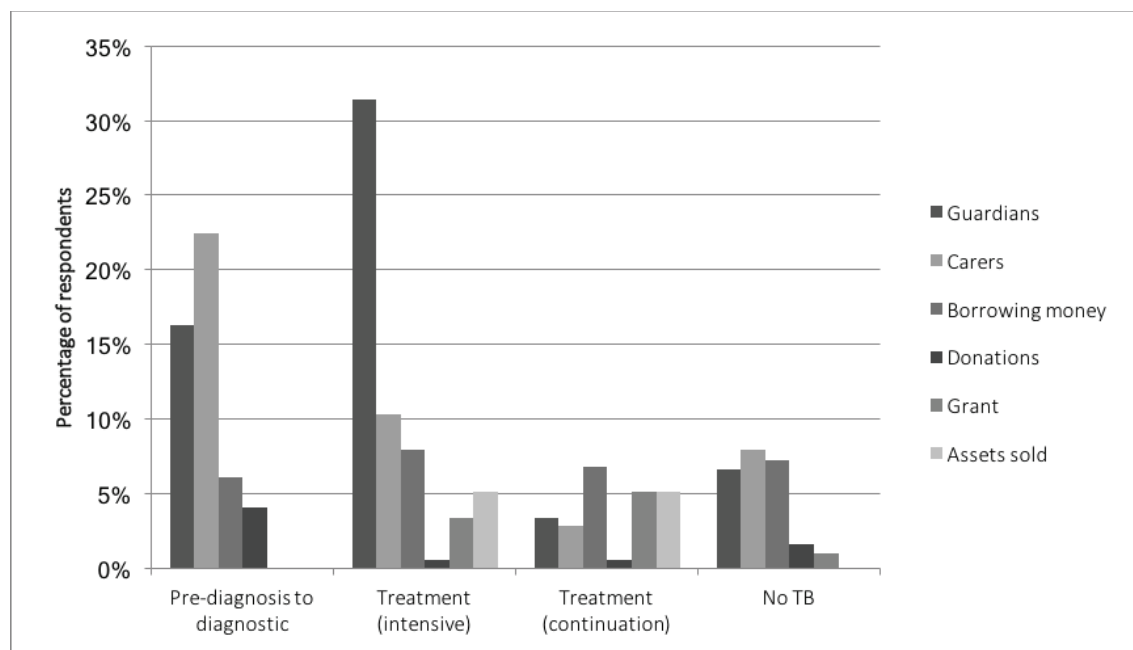


Figure 19. Percentage (%) of respondents using coping strategies (stratified by type) at different points in the pathway.

About 22% of those with TB compared to 8% of those with TB reported relying on carers, either in the form of someone to take over their job or household duties or to look after them prior to starting and during treatment, and 5% of patients reported selling assets. We found that few patients (3%) were accessing cash transfers (in the form of the disability grant) during the intensive phase of treatment with a subsequent slight increase (to 5%) during the continuation phase of treatment. This may reflect the time it takes from application to receiving the grant and suggests a lack of access to grants. We explored factors associated with incurring catastrophic health expenditure in Table 10 below.

Table 10. Regression exploring relationship between 'catastrophic' health care related expenditure (>10% of annual individual income) and key socio-economic and related factors.

Variable	Diagnostic period		Treatment period	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender (1 = male)	1.20 (0,69; 2,10)	0.521	0.35 (0,17; 0,73)	< 0.05
Rural (1 = rural)	0.98 (0,53; 1,81)	0.950	2.67 (1,22; 5,85)	< 0.05
TB (1 = positive)	1.28 (0,60; 2,75)	0.528	-	-
Number of symptoms	1.18 (1,02; 1,36)	< 0.05	-	-
Number of health care visits	1.10 (1,01; 1,21)	< 0.05	0.99 (0,98; 1,01)	0.242
Main source of income = No income	reference		reference	
Main source of income = Formal	0.17 (0,07; 0,40)	< 0.05	0.34 (0,12; 0,98)	< 0.05
Main source of income = Self-employed	0.22 (0,05; 0,97)	< 0.05	0.70 (0,14; 3,59)	0.670
Main source of income = Odd jobs	0.66 (0,30; 1,46)	0.304	0,46 (0,14; 1,56)	0,213
Main source of income = Government grant	1.23 (0,58; 2,61)	0.584	1,04 (0,41; 2,60)	0,937
Asset index (1 = least poor)	1.26 (0,69; 2,28)	0.453	0.67 (0,31; 1,47)	0.315
Years of schooling	1.01 (0,93; 1,10)	0.837	1.01 (0,90; 1,12)	0.926
Amount spent on nutritional supplements	1.00 (1,00; 1,01)	< 0.05	1.12 (1,02; 1,24)	< 0.05
	Pseudo R2 = 0.1651		Pseudo R2 = 0,1959	

Not surprisingly, we found that those who reported that their main source of income was through formal or self-employment, as compared to those with no income, were less likely to experience catastrophic expenditure. During the diagnostic phase, the number of symptoms and health care visits were significant factors in catastrophic expenditure. In both the diagnostic and treatment phase the amount spent on nutritional supplements increased catastrophic expenditure.

5.4 Discussion and conclusion

The study found that the cost of TB diagnosis and treatment in South Africa could be catastrophic and drive the 'medical poverty trap'. For those starting on treatment, the costs associated with a TB episode totalled 22% of the average pre-symptomatic individual income. The greatest financial cost was incurred in the time between first becoming symptomatic and starting treatment. A similar trend was found in other patient cost studies where pre-treatment and treatment costs were included (197,298). This was compounded by the income loss experienced prior to treatment, which made up 72% of the total episode income loss and 26% of the total episode cost. This is significant given

that 59% of respondents reported no income prior to symptoms. Where we used a proxy to compare costs against a nominal income of US\$1 per annum, the percentage of costs against income is seen to exceed income which suggests that those with no income are experiencing excessive out-of-pocket costs, placing a significant burden on households given that only approximately a third of respondents indicated that another household member had a steady job.

Geographical access to health facilities was good, with few reported visits to private health facilities or Traditional Health Practitioners (THP) before receiving a TB test. Only 3% of respondents reported visits to THP, this is possibly underreported due to social desirability bias (299). While the relatively low levels of direct costs were encouraging, we found that for many patients these small expenses were nevertheless catastrophic given that many patients reported no income. Where individuals did report having an income, income loss when patients started experiencing TB symptoms was high and may have been influenced by a lack of the protective effects of sickness benefits and leave when employed in the informal sector.

Given that the number of health care visits was a significant factor in determining catastrophic expenditure, the South African Department of Health's policy on reducing the number of visits to a health facility during TB treatment has alleviated some of the economic burden (300). However, without proper support, a reduction in visits may have consequences for adherence and future drug resistance. The system of TB treatment through community-based care has been shown to be cost-effective and has been policy for many years; but has yet to be implemented in a comprehensive manner (209). Further effort should be made to strengthen and implement this policy.

Coping strategies and social networks triggered by these financial stresses were activated in a cascade. During the symptomatic and intensive phase of treatment, patients were relying on guardians and carers for assistance, and borrowing money was greatest during the intensive phase of treatment. Conversely, uptake of cash transfers only occurred during the continuation phase of treatment when the economic burden on individuals was at its lowest. In South Africa, a short-term cash transfer, called the disability grant is provided to individuals if they are deemed to be unable to work because of a physical disability. Access to these grants is however limited as patients must see a dedicated

doctor who is not based at the clinic (personal communication, South African Social Security Agency). This is reflected in our results, with only 5% of respondents receiving a disability grant. The percentage of patients selling assets increased between the pre-treatment period and the continuation phase of treatment, as financial losses over time depleted household as well as social resources (200). The proportion of patients borrowing money and selling assets was like what was found in another South African study (289).

The study had several limitations. Firstly, recall bias is a concern in patient cost surveys. Although we have improved upon previous methods by conducting a longitudinal study, a balance had to be found between ensuring the ‘pragmatic’ nature of the research setting was retained and recall bias. We attempted to limit the negative effect of recall bias by linking questions about costs incurred to ‘memorable’ events such as starting treatment or the start of symptoms. A second limitation of the study is that even though we attempted to capture the influence on social networks, assessing the impact on the household through patient - rather than household surveys may not fully capture the household impact of the cost of illness. For example, it was not possible to collect accurate household income data, and by comparing the direct costs incurred against annual individual income, we might have underestimated the burden of the cost given that individual income is likely to be shared among members of a household. It is also possible that household members would share their income with the respondent, although this effect may be small as only a third of respondents reported that another family member had a steady job. In addition, the impact of a single disease was studied, and further research should be done to estimate the economic burden to patients with multiple chronic diseases especially co-infection with HIV and TB. And lastly, due to the nature of the study, we were only able to interview those who, by definition, could access health services. It is therefore possible that we are underestimating the access barriers due to out of pocket cost and income losses. Although the findings are limited in the sense that they are pertinent to South Africa, the general approach used by this study could be applied to other settings; the use of longitudinal data, the measurement of income loss and including the costs to societal networks.

Nevertheless, some important policy recommendations can be made. Firstly, the social protection scheme as it currently stands is not sufficient to alleviate the poverty impact

of TB and prevent TB by minimising poverty. It was encouraging to find that most patients' first point of call when ill was a public clinic, and that patients were largely able to walk to a health facility. However, even though TB services are provided free of charge, patients are incurring catastrophically high costs. Many patients had little or no income with which to pay for these costs. The social protection currently provided comes in too late. Although there have been calls to reduce the 'holes' in the social protection safety net in South Africa, this remains a long-term solution (301). More comprehensive social protection programs, that cover more than just the direct costs of care but also allow for better nutrition and prevent households from being further impoverished by illness are needed. In the short term, the priority for poverty focused TB services must be the early detection of TB. Many of those with TB are currently in HIV care, and therefore policies supporting intensive case finding in these groups may have a poverty alleviating impact. For those accessing general health services, integration of TB screening into primary health care services would be beneficial. Once on treatment, providing treatment and support in the community would reduce the impact of TB on household members especially during the intensive phase of treatment. Access to the current disability grant could be improved by removing the need for assessment by a doctor.

People with suspected TB and those on TB treatment were followed up over a sustained time to examine the economic burden of TB in South Africa. The results highlight the importance of including those with no incomes in the analysis and the mismatch between the need and availability of social protection for those with TB. We found that respondents incurred high economic losses prior to diagnosis and that income loss was severe. Both national and global policy recommendations should therefore focus on ensuring that health systems identify those with TB early on, support those on treatment with TB in a way that minimises income loss and provide social protection to those with the lowest income if we are to break the vicious cycle between TB and poverty for those living in deprived circumstances.

Additional figures

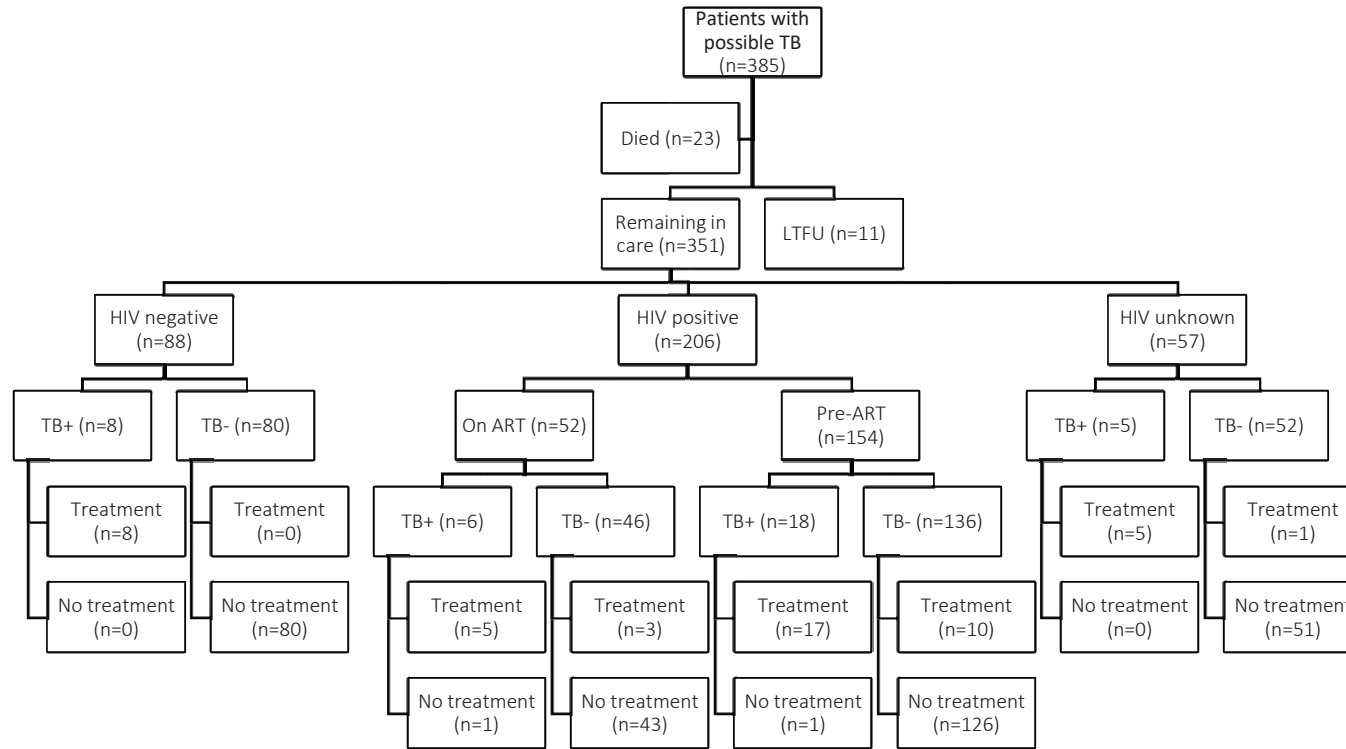


Figure 20: Patient outcomes of the TB suspect cohort

In the table, LTFU represents the patients who became lost to follow-up; TB+ and TB- refers to those who received positive TB test result and those who received a negative TB test result respectively; ART stands for anti-retroviral treatment.

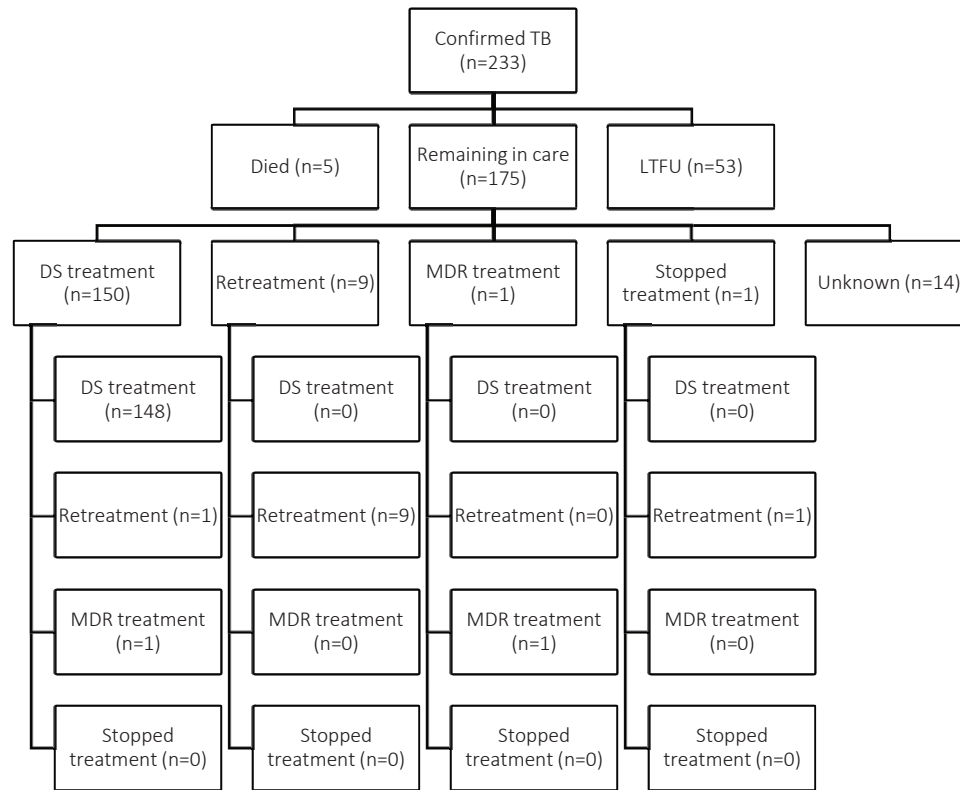


Figure 21: Patient outcomes of the confirmed TB cohort

In the table, LTFU represents the patients who became lost to follow-up; TB+ and TB- refers to those who received positive TB test result and those who received a negative TB test result respectively; ART stands for anti-retroviral treatment.

CHAPTER 6: COST-EFFECTIVENESS OF INVESTMENTS TO SUPPORT TB DIAGNOSIS

Summary

South Africa was an early-adopter of Xpert MTB/RIF for TB diagnosis; however, studies conducted during implementation found that the Xpert-based TB-diagnostic guideline did not reduce mortality when compared to microscopy, though was found to be cost-neutral (12). As Xpert is efficacious, variation in implementation is hypothesised to have resulted in the lack of improvement in outcomes. A mathematical model was developed to explore how complementary investments may improve the value of the algorithm by strengthening supportive structures for the implementation of Xpert MTB/RIF. Complementary investments in the patient pathway were compared to the status quo (Xpert MTB/RIF). Scenarios assessed included actions to reduce initial pre-treatment loss-to-follow-up (iLTFU); supporting empirical TB treatment; and improving access to further diagnostic tests following a negative result (negative pathway)). We estimated costs, deaths - and disability-adjusted-life-years (DALYs) averted per scenario from a societal perspective. Sensitivity analyses explored the influence of behavioural, disease and organisational characteristics that potentially mediate the effectiveness of all investments. Among a population of symptomatic patients in South Africa with a TB prevalence of approximately 13%, 45% HIV prevalence, and who are tested for TB, reducing iLTFU led to a 4% reduction in mortality compared to the observed 'status quo' scenario, while improving the pathway for further testing after a false negative test result reduced mortality by 14%. Effectiveness of investment in the negative pathway was dependent on ensuring a high rate of return for follow up visits. Up to an additional \$600 per patient could be invested in health systems strengthening to support implementation of the TB diagnostic algorithm without crossing a revealed WTP cost-effectiveness threshold. Investing in both direct and indirect complementary investments to support progression along the TB diagnostic pathway is potentially highly cost-effective. Our study demonstrates an approach to determine the optimal investments to support new diagnostic technology introduction in different settings.

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6.1 Introduction

Globally, there is renewed interest in understanding how disease-specific investments function in the context of broader health system challenges (302). Alongside this interest, is re-invigorated enquiry into how best to support policy makers to assess joint technology and health systems strengthening investments when introducing new technologies. A recent example of an investment with global importance is the roll-out of Xpert MTB/RIF (Xpert). In 2011, the South African Minister of Health announced the national roll out of Xpert as the first line TB diagnostic test in South Africa, following recommendations from the World Health Organisation (WHO) (303). Early demonstration studies in South Africa suggested that Xpert would be more sensitive in detecting TB in HIV-positive individuals than the previous standard of care, smear microscopy (304). Xpert was expected to provide results more quickly and have the added benefit of diagnosing Rifampicin-resistant TB (RR-TB), an indicator for multi-drug resistant (MDR) TB. Model-based analyses suggested that Xpert was likely to be cost-effective due to improved diagnostic sensitivity or through generating downstream cost savings, depending on assumptions about the sensitivity and specificity of the standard of care in starting those with TB on treatment (80,234).

However, studies conducted following the implementation of Xpert found no significant impact on TB related morbidity, mortality, initial loss-to-follow-up (iLTFU) or time to treatment for patients starting drug-sensitive TB (DS-TB) treatment during the early stages of roll-out in South Africa (12,305). Where studies specifically examined the impact on patients with multi-drug resistant (MDR) TB, they found that Xpert reduced the time to appropriate treatment, though not to same day or same week, as had been expected (306,307). Furthermore, an economic evaluation based on a pragmatic trial following the roll-out in South Africa (the XTEND trial) found that Xpert implementation during early roll-out was both effect and cost-neutral and was unlikely to improve the cost-effectiveness of the TB diagnostic algorithm (308). The study concluded that implementation constraints may have mediated the impact of Xpert under programmatic conditions (81,309). The lack of improvement in patient outcomes observed following Xpert implementation has been hypothesized by some to be as a result of TB treatment being started empirically following a negative smear microscopy result. The discrepancy

between modelled and observed population impact might also suggest that the baseline standard of care was better than could be predicted when parameterising models primarily using the diagnostic accuracy (222,309). Other countries have reported similar experiences from the implementation of Xpert (224,226,310–315). The placement of the test in the health system, how it is integrated into the available laboratory infrastructure and diagnostic algorithm, as well as patient linkages to treatment were found to be important mediators of costs and effects.

For South Africa and beyond, there is therefore a need to support policy makers to determine which complementary investments are required to realise the potential benefits of Xpert, and other TB diagnostics. To inform this need and illustrate a potential approach to assessing combined diagnostic technology and health systems investments, we calibrated a purpose-built mathematical model, the SINDI model, to empirical data from the XTEND trial (12). We then explored which complementary investments to the Xpert-based diagnostic algorithm would be most cost-effective in South Africa and used the model to identify the contextual drivers influencing the cost-effectiveness of these investments. For South Africa and beyond, there is therefore a need to support policy makers to determine which complementary investments are required to realise the potential benefits of Xpert, and other TB diagnostics. To inform this need and illustrate a potential approach to assessing combined diagnostic technology and health systems investments, we calibrated a purpose-built mathematical model, the SINDI model, to empirical data from the XTEND trial (12). We then explored which complementary investments to the Xpert-based diagnostic algorithm would be most cost-effective in South Africa and used the model to identify the contextual drivers influencing the cost-effectiveness of these investments.

6.2 Methodology

A cost-utility analysis of health systems investments to support TB diagnosis was conducted. This analysis builds on previous modelling work that explores investments in patient pathways (153,228,251,316) by using patient-level longitudinal data from a pragmatic cluster randomised control trial (described in Chapter 4).

6.2.1 Overview of the conceptual approach

Health systems investments are typically conceptualised as investments in health care infrastructure, clinical guidelines, technology or human resources, with less emphasis on how the relational aspect of health systems (317) may affect the costs and outcomes of an investment. Clinical discretionary decision-points in patient care can be conceptualised as transactions between the provider and the patient, occurring within a given organisational system. One may consider these transactions as interactions between the hardware - and software components of health systems (318). Hardware components of the system include technology, infrastructure and finances; while the tangible software components refer to the formal or informal organisational rules of practice (including clinical guidelines). Intangible software refers to the values and beliefs that unite the organisation and explain behaviour. While some have estimated costs of investments by analysing how the production of healthcare responds to an increase in need (319,320); in this analysis, we identify patterns of provider behaviour and then model this behaviour as a function of resource availability, processes or relational interactions. This is implemented in the model by the mediation of decisions along the patient pathway, and by exploring how investment scenarios may be mediated (see Figure 22) (321). The costs of the decision-making process includes the cost of regulating the decision as well as the opportunity cost of the benefits forgone in the time taken to make the decision or in making the wrong decision, the transaction cost (31: 86). We estimate the value of additional investments that can be made to strengthen these decision-making processes, defined as the difference between the ICER and the CET. Secondly, we describe how the transaction cost incurred at each decision changes the prioritisation of investment scenarios.

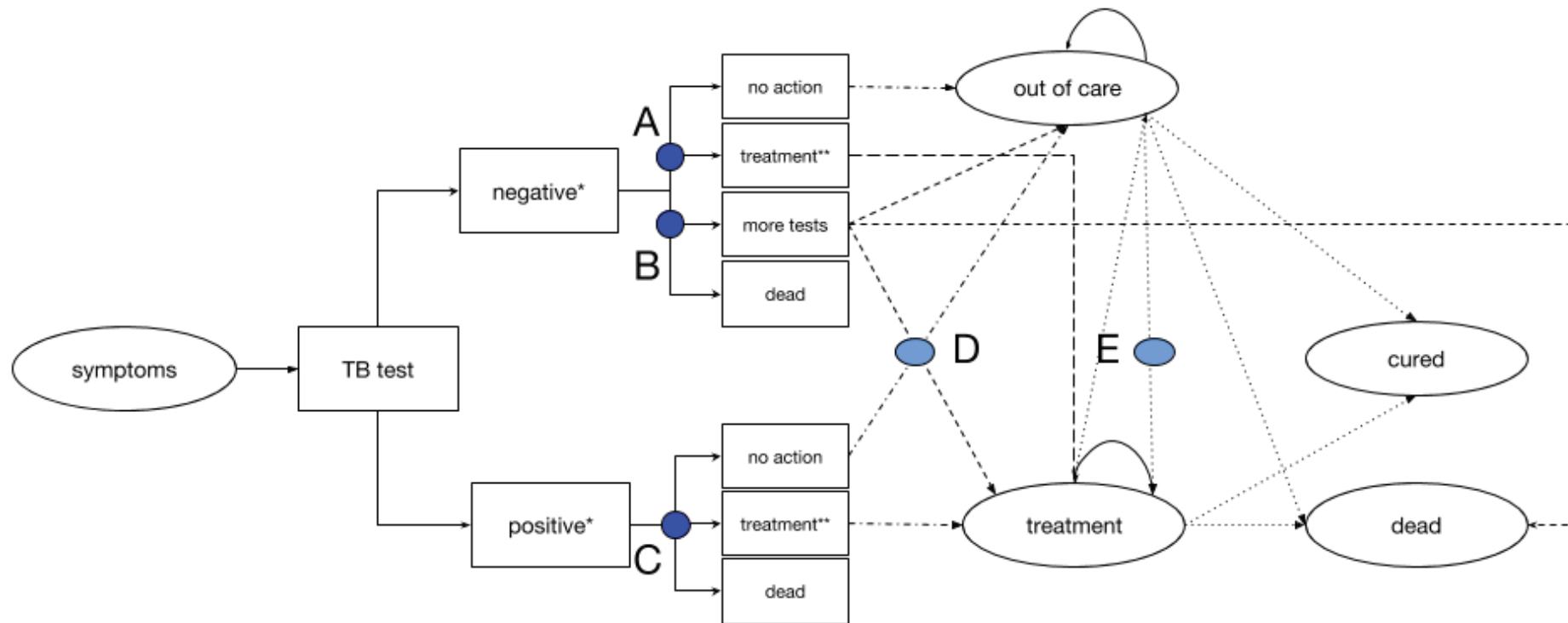


Figure 22. Simplified schematic of the SINDI model developed and used in the analysis.

The figure is a simplified representation of the model, with the circular boxes representing health states and the square boxes representing intermittent states used to model shorter time step processes, the model structure is presented in more detail in Figure 8. “A” refers to the decision-making process from a negative test result to starting treatment without a bacteriological confirmation; “B” represents the decision to continue testing for TB (negative pathway) in those with a negative test result; C is the behaviour around starting treatment after a positive test result; D refers to the decision (based on an interpretation of the further diagnostic tests) to start treatment; and E refers to the decision to start TB treatment after being ‘out of care’. * The model structures following the TB test is replicated for each of the six patient types, those HIV negative (with and without TB), HIV positive not on ART (with and without TB), and those HIV positive on ART (with and without TB). ** The treatment states are replicated for drug-sensitive treatment and drug-resistant TB treatment.

6.2.2 Mathematical model

A state-transition model with time-dependent Markov processes, the SINDI model, was developed (described in further detail in Chapter 4). The model simulates disease progression and interactions with the health system in a symptomatic population investigated for TB. The secondary benefits to the population through TB transmission reduction is not included (219). The timeframe of the analysis is three years, representing the time until the population is either cured of this episode, or dead. A cycle length of one month was used to account for the slightly longer processes of treatment and movement from out of care, with additional structure added to model diagnostic processes with smaller time steps. The model was implemented in TreeAge Pro 2018 and parameters estimated using STATA 13.

In the model, six discrete types of patients defined by HIV, ART and true TB status, move through health states until reaching an absorbing state (cure or death). Patients enter the model symptomatic and if identified as needing a TB test by primary health care staff (TB screen positive), transition through a series of diagnostic processes, following which they move to one of four possible health states (1) 'out of care' if not started on treatment; (2) treatment (drug sensitive or MDR treatment); (3) death; or (4) cured; which can be entered either after treatment or based on a self-cure rate from out of care in those with TB.

Table 11. Summary of parameters and distributions.

Definition	Mean (standard deviation) and stratification	Distribution	Comments. References are listed as name of first author, year (Reference).
Population			
Gender	59.9% female		Represents trial population. Churchyard. 2015 (12)
Age (IQR)	37 (29 - 48) years	Fixed	Represents trial population. Churchyard. 2015 (12)
Initial population disease characteristics	HIVneg 0.314 (0.030); HIVpos 0.531 (0.015); ART 0.155 (0.005)	Dirichlet	From trial population. Churchyard 2015 (12) Those with unknown self-reported HIV status are assumed to be HIV positive, not on ART.
CD4 count in those with HIV (IQR)	315 (192 - 480) cells/ μ L		Represents the trial population. Churchyard. 2015 (12)
True TB prevalence (includes bacteriologically confirmed -, clinical - and undiagnosed TB)	18.0%	Fixed	Estimated from XTEND trial and model calibration. Churchyard. 2015 (12)
Proportion of patients diagnosed with drug-resistant TB, any diagnosis	4.0% (8/195)		Represents trial population. Churchyard. 2015 (12).
Proportion of patients starting MDR TB treatment	2.0% (3/195)		Represents what was observed in the XTEND trial. Churchyard. 2015 (12). Time to starting MDR TB treatment was 11 and 33 days respectively.
Diagnosis, transition probabilities			
Probability of a positive Xpert test result if symptomatic and able to provide a sputum sample	HIVneg 0.077 (0.03); HIVpos 0.132 (0.05); ART 0.135 (0.03)	Dirichlet	Churchyard. 2015 Estimated from XTEND trial. Churchyard. 2015 (12)
Probability of TB if patient had a positive test result	HIVneg 0.877; HIVpos 0.936; ART 0.938	Fixed	Estimated based on GX sensitivity 0.86 in HIVneg; 0.79 in HIVpos, 0.94 for Rif resistance, and GX specificity of 0.99 in HIVneg, HIVpos, 0.98 for Rif resistance. Steingart 2014 (322), Steingart 2006 (323), and Boehme 2011 (324).
Probability of TB if patient had a negative test result	HIVneg 0.012; HIVpos 0.113; ART 0.114	Fixed	Unobserved parameter estimated from model calibration. Based on GX sensitivity 0.86 in HIVneg; 0.79 in HIVpos, 0.94 for Rif resistance, and GX specificity of 0.99 in HIVneg, HIVpos, 0.98 for Rif resistance. Steingart 2014 (322), Steingart 2006 (323), and Boehme 2011 (324). This includes a probability of a false negative test result; HIVneg 0.012; HIVpos pre-ART 0.038; HIVpos ART 0.039 as well as a probability of 'undiagnosed TB'. Undiagnosed TB includes those who provide pauci-bacillary sputum or have extra-pulmonary TB.
Probability of starting treatment within 30 days of a positive test result	HIVneg 0.882 (0.325); HIVpos 0.802 (0.400); ART 0.944 (0.236)	Dirichlet	Estimated from XTEND trial. Churchyard et al. 2015 (12)
Probability of starting treatment within one month of a negative test result without further diagnostic tests (empirical treatment)	HIVneg_TB 0.535; HIVneg 0.002; HIVpos_TB 0.072; HIVpos 0.009; ART_TB 0.017; ART 0.003	Fixed	Probability of starting treatment was estimated from XTEND trial, whether this clinical decision was correct (treatment started in those with TB vs those without) was estimated through model calibration. Churchyard et al. 2015 (12). We therefore assume that clinicians are unlikely to start treatment empirically in those HIV negative.
Probability of receiving further investigations after a negative test result (negative pathway)	HIVpos_TB 0.041; HIVpos 0.041; ART_TB 0.073; ART 0.073	Fixed	McCarthy. 2016 Estimated from XTEND trial. Churchyard. 2015 (12,272).
Probability of starting TB treatment after further diagnostic tests (negative pathway)	HIVpos_TB 0.212; HIVpos 0.027; ART_TB 0.217; ART 0.037	Fixed	Estimated from XTEND trial and the model calibration. Churchyard. 2015. McCarthy. 2016 (12,272).
Probability of starting TB treatment from 'out of care', by month: from all who do not start TB treatment within one month of the diagnostic test			

month 2	HIVneg_TB 0.928; HIVneg 0.005; HIVpos_TB 0.164; HIVpos 0.000; ART_TB 0.100; ART 0.000	Fixed	Curve estimated from XTEND trial. Assume that the behaviour from out of care remains the same (12).
month 3	HIVneg_TB 0.756; HIVneg 0.000; HIVpos_TB 0.066; HIVpos 0.000; ART_TB 0.207; ART 0.000	Fixed	Curve estimated from XTEND. Assume that the behaviour from out of care remains the same. Churchyard. 2015 (12).
month 4	HIVneg_TB 0.000; HIVneg 0.005; HIVpos_TB 0.146; HIVpos 0.000; ART_TB 0.148; ART 0.000	Fixed	Curve estimated from XTEND. Assume that the behaviour from out of care remains the same. Churchyard. 2015 (12).
month 5	HIVneg_TB 0.000; HIVneg 0.015; HIVpos_TB 0.064; HIVpos 0.000; ART_TB 0.000; ART 0.000	Fixed	Curve estimated from XTEND trial. Assume that the behaviour from out of care remains the same. Churchyard. 2015 (12).
month 6	HIVneg_TB 0.000; HIVneg 0.010; HIVpos_TB 0.060; HIVpos 0.000; ART_TB 0.000; ART 0.000	Fixed	Curve estimated from XTEND trial. Assume that the behaviour from out of care remains the same. Churchyard. 2015 (12).
Probability of starting DR-TB treatment if diagnosed with DR-TB	HIVneg 0.025; HIVpos 0.019; ART 0.000	Dirichlet	Estimated from XTEND trial. Churchyard. 2015 (12).
<u>Treatment, transition probabilities</u>			
Probability of drug sensitive TB regimen started if TB treatment started	HIVneg 0.952; HIVpos 0.969; ART_TB 0.834	Dirichlet	Estimated from XTEND trial. Churchyard. 2015 (12).
Probability of MDR-TB regimen started if TB treatment started	HIVneg 0.039 (0.208); HIVpos 0.023 (0.002); ART 0.000 (0.000);	Dirichlet	Estimated from XTEND trial. Churchyard. 2015 (12).
<u>Disease progression, transition probabilities</u>			
Average life expectancy at birth, South Africa	63 years	Fixed	From the rapid mortality surveillance report 2014. Assume that HIVpos patients who are on ART when they enter the model, would have the same life expectancy as the general population (varied in the sensitivity analysis). HIV specific mortality considered in model through probabilities. Dorrington. 2015. (325) Years of life remaining at death is estimated from the difference between current age in model (mean age of cohort + time in model) and the average life expectancy at birth.
All-cause mortality in those without TB, monthly	HIVneg 0.001 (0.0005); HIVpos 0.002 (0.000); ART 0.001 (0.001)	Dirichlet	From Statistics South Africa report (P0309.3), mortality and causes of death in South Africa: findings from death notification (326).
Mortality if living with TB, not currently receiving treatment, monthly	HIVneg 0.018 (0.020); HIVpos 0.132 (0.005); ART 0.039 (0.005)	Changes over time	Based on Tiemersma. 2011.(327) Used half-cycle correction to adjust for earlier movement into treatment in month 1 of the model.
Mortality on treatment for those with TB, monthly	HIVneg 0.002 (0.001); HIVpos 0.046 (0.002); ART 0.006 (0.003)	Changes over time	Andrews 2012 (328). Mohr 2015 (329). Monthly mortality reduction due to TB treatments added as distribution over time, where mortality reduces to 10% of the mortality of those with TB not on treatment at month 5 on treatment. Based on comparison with mortality on treatment observed in the XTEND trial. Churchyard 2015 (12).
Disability weights	HIVneg_TB 0.331 (0.057); HIVpos_TB 0.399 (0.070); HIVpos 0.221 (0.041); ART 0.053 (0.011); ART_TB 0.331 (0.057)	Beta	Salomon. 2015 (266). Kastien-Hilka. 2017 (330). Assuming that disability weights are not cumulative, thus those on ART with TB has the same disability weight as someone with TB disease only.
<u>Cost and resource use</u>			
Microscopy (FM)	\$ 6.30 (\$ 1.34)	Gamma	Cunnama 2016.(165)
Xpert MTB/RIF	\$ 16.90 (\$ 6.10)	Gamma	Cunnama 2016.(165)

Sputum liquid culture	\$ 12.90 (\$ 2.26)	Gamma	Cunnama 2016. (165)
Digital CXR	\$ 15.17 (\$ 7.74)	Gamma	Foster. Unpublished.
First-line drug sensitivity test (LPA)	\$ 20.30 (\$ 7.28)	Gamma	Cunnama 2016. (165)
Second-line drug sensitivity test	\$ 25.10 (\$ 20.22)	Gamma	Cunnama 2016. (165)
Provider cost of clinic visit for initial diagnosis and monitoring	\$ 8.63	Fixed	Vassall 2017. (331)
Provider cost of clinic visit for treatment	\$ 3.89	Fixed	Vassall 2017. (331)
Patient cost of clinic visit	\$ 2.90	Fixed	Foster 2015. (198)
Guardian cost per clinic visit	\$ 10.04	Fixed	Foster 2015.(198)
Cost of caregiver per day	\$ 0.69	Fixed	Foster 2015. (198)
Resource use along the diagnostic pathway	Detailed input available from S2 Data.	Gamma	Estimated by disease progression. Reported in Vassall 2017. Foster 2015. (198,331).
Provider cost of DSTB treatment, episode	\$ 192.99	Time-dependent functions	Estimated based on disease progression from trial (see Figure S5). Reported in Vassall 2017 and Foster 2015. (198,331)
Provider cost of MDR treatment, episode	\$ 10 802.66	Time-dependent functions	Estimated based on disease progression from trial (see Figure S5). Reported in Vassall 2017 and Foster 2015 (198,331)
Patient cost of DSTB treatment, episode	Cost of accessing care associated \$ 459.16; Cost of illness \$ 135.94	Time-dependent functions	Foster 2015. (198)
Patient cost of MDR treatment, episode	Cost of accessing care associated \$ 3 592.27; Cost of illness \$ 2 442.03	Time-dependent functions	Foster 2015. (198)

In the Table, where a distribution is called fixed, it refers to one where no uncertainty interval added to the distribution; and is common practice for calibrations of complex models. Where IQR = interquartile range; HIVpos = individuals HIV positive not yet started on ART; HIVpos_TB = individuals HIV positive with TB; ART = individuals HIV positive started on ART; ART_TB = individuals HIV positive on ART with TB. The full parameter list upon which this Table is based, is available in the supplementary materials.

6.2.3 Parameter estimation and model calibration

Transition probabilities, resource use, unit costs and associated parameter uncertainty were estimated from trial data (summarised in Table 11). Where treatment-related events occurred after the six-month trial period, data from published cohorts and meta-analyses were used to construct the patient pathway until the end of the treatment episode. The pragmatic nature of the trial did not allow for definitive confirmation of TB diagnosis among all trial participants. Therefore, unobservable parameters include the true TB prevalence in the population, as well as the predictive value of decisions to start treatment or request further investigations. These parameters were estimated by calibrating the model's mortality and treatment outputs against those observed in the trial (264). We estimated a plausible range of values for each of the unobserved parameters and then iteratively calibrated the mortality and time-to-treatment curves from model outputs to the Kaplan-Meier curves from the trial until the shape of the respective curves fitted using a range of goodness-of-fit measures (230:260). The calibration procedures are described in Chapter 4.

6.2.4 Cost analyses

The costs of providing and accessing care were estimated alongside the trial and included provider -, patient -, laboratory and above service-level costs estimated using a combination of top-down and ingredients costing approaches and reported in detail elsewhere (233,258,259). The costs associated with HIV care were extracted from published sources (Table 11). Provider costs were estimated by multiplying unit costs by the number of events incurred by patient type from data collected during the trial, implementing time-varying costs. The cost incurred by patients include travel - and time costs incurred by patients and caregivers when accessing care. Costs incurred due to illness included income loss, the cost of caregiver's time, interest on loans as well as the cost of nutritional supplements. The opportunity cost of time was valued by multiplying time loss by the pre-illness mean income of the cohort (198). All costs were estimated in local currency using 2013 prices and converted to US dollars using the average 2013 exchange rate of US\$1=R9.62 (www.Oanda.com).

6.2.5 Investments

The pragmatic nature of the trial enabled us to identify the gap between ideal movement along different decision nodes of the pathway and current mediating variables of effectiveness in routine care settings (summarised in Table 12).

Based on these insights, we modelled three investment strategies to support TB diagnosis. These included (1) reducing initial loss-to-follow-up (iLTFU), (2) changing the extent to which TB treatment is started in the absence of bacteriological confirmation (empirical treatment), and (3) providing additional diagnostic tests after an initial negative test result (negative pathway). Investments were implemented by altering process variables at key stages in the patient pathway.

Table 12. Summary of the investment designs.

	Investment	Model implementation	Parameter, events or resource changes	Assumptions
Reduction in initial LTFU (in Figure 1; decision-point C and E)	All patients with positive TB test results start treatment within one month of testing - simulating a point-of-care or a track-and-trace scenario with active follow-up of people with a positive TB test result. Synergies with investment in a community health worker programme.	ptxfpos = 1 - pMort_m1 (stratified by HIV and TB status) The probability of starting treatment from a positive test result was the remainder of all patients in that state after those who would die in that month had been subtracted. The mortality rate was stratified by HIV and TB status.	Probability of starting treatment after positive (in month 1), from: HIVneg: 0.882 to 1; HIVneg_TB: 0.882 to 1; HIVpos: 0.802 to 1; HIVpos_TB: 0.802 to 1; ART: 0.944 to 1; ART_TB: 0.944 to 1	Monthly conditional probabilities of starting treatment from 'out of care', was estimated from the trial in the base scenario (reported in Table 1). In this investment scenario, patients shift from moving to the 'out of care' state if not started on treatment within one month, to the treatment state immediately, thus probabilities of starting treatment from 'out of care' approximates zero. The relative proportions of those starting various treatment types is kept the same as observed in the trial.
Empirical treatment from negative test result (in Figure 1; decision-point A)	The ability of healthcare workers to correctly act (by giving TB treatment to those with test negative TB expressed as the sensitivity and specificity of that decision) based on continued clinical symptoms, on the same day as the results visit. This was based on the behaviour estimated during the microscopy arm of the model calibration and was applied to behaviour after a negative Xpert test result.	pnegpathfeg = 0 ptreatfneg = value estimated from reported behaviour in the control arm of the XTEND study (332), under the assumption that behaviour observed after the implementation will revert back to pre-implementation levels. Assumed that all have at least one visit to a public health clinic (and associated costs) after a negative test result for treatment initiation.	Probability of the negative pathway after a negative test result , from: HIVpos: 0.027 to 0.000 HIVpos_TB: 0.212 to 0.000 ART: 0.037 to 0.000 ART_TB: 0.217 to 0.000 Probability of starting treatment after negative , from: HIVneg: 0.002 to 0.040 HIVneg_TB: 0.054 to 0.270 HIVpos: 0.009 to 0.180 HIVpos_TB: 0.072 to 0.360 ART: 0.003 to 0.060 ART_TB: 0.017 to 0.090	Given the differences in health care worker behaviour after a microscopy test compared to a Xpert test result observed in the XTEND trial, we use the calibrated transition probabilities estimated for the microscopy arm of the trial (333,334).
Improvements in the negative pathway (in Figure 1 decision-points B and D)	Those HIV positive with negative test results get further investigations (CXR/culture) for possible TB, and a proportion are started on TB treatment, simulating additional investment in improving access to further diagnostic tests.	ptreatfneg = 0 pnegpathfeg = 1 (stratified by HIV and TB status) treatfnegpath = 0.10 (no TB); 0.80 (with TB) The probability of starting treatment is shifted from following a negative test result to the decision to order further diagnostic tests. The negative - and positive predictive values estimated from the trial are assumed to stay the same. The probability of starting treatment after the negative pathway was 10% in those without TB, and 80% in those with TB.	Probability of starting treatment after negative changes from: HIVneg: 0.002 to 0.000 HIVneg_TB: 0.054 to 0.000 HIVpos: 0.009 to 0.000 HIVpos_TB: 0.072 to 0.000 ART: 0.003 to 0.000 ART_TB: 0.017 to 0.000 Probability of the negative pathway after a negative test result change from: HIVpos: 0.041 to 0.900 HIVpos_TB: 0.041 to 0.900 ART: 0.073 to 0.900 ART_TB: 0.073 to 0.900 Probability of treatment from negative pathway changes from: HIVpos: 0.027 to 0.000	Similar to the previous scenario, we model a behaviour change scenario based on the difference in observed behaviour between the microscopy and Xpert arms of the study. This scenario simulates a situation where all receive further investigations after a negative test result. Therefore, we reduced all empirical treatment to 0 and all eligible patients received a CXR, as part of the negative pathway. The proportion of those who receive further diagnostic tests was assumed to be similar to that observed in the microscopy arm of the XTEND study.

Assumed that every person will accumulate two visits to the public clinic during the negative pathway implementation, and that each person getting further tests will get at least one CXR.

HIVpos_TB: 0.212 to 0.846
ART: 0.037 to 0.000
ART_TB: 0.217 to 0.846

In the Table, the individual characteristics of the patients are labelled as HIVneg for people who are HIV negative; HIVneg_TB for people who are HIV negative and has been diagnosed with TB; HIVpos for people who are HIV positive; HIVpos_TB represents people who are HIV positive and has been diagnosed with TB; ART represents the individuals who are HIV positive and on ART; and ART_TB represents the individuals who are HIV positive, on ART and has been diagnosed with TB.

6.2.6 Economic analyses

The cost-effectiveness and cost-utility of investment scenarios are estimated from a provider – and societal perspective. The societal perspective includes the provider costs as well as the cost to patients. Disability Adjusted Life Years (DALYs) averted were estimated using the model estimates of years of life lost (YLL) due to premature mortality and years lived with disability (YLD). YLL were estimated based on progression through the model, assuming an average life expectancy of 63 years and based on the mean age of patients in the trial of 38 years (12,325). Disability weights from the 2010 Global Burden of Disease study were attached to progression through stages in the model, based on patient disease characteristics (335). For people on ART with TB, we assumed the same disability weight as for those with TB who are HIV negative. Costs and outcomes were discounted at 3% per annum, and varied in the sensitivity analysis (35: 108 - 112).

Changes in the optimal investment at a range of transaction costs, the costs generated by the way in which health services are structured, is presented by plotting cost-effectiveness acceptability frontiers (CEAF) (336). The CEAF presents the optimal investment option, defined as the strategy with the highest net monetary benefit (NMB), a statistic of the monetary value of an investment at a given cost-effectiveness threshold (λ).

6.2.7 Sensitivity and scenario analyses

The impact of variation in individual models' parameter on the results in the model was assessed through univariate sensitivity analysis (see Table 15). Probabilistic uncertainty analysis, simulating 100 000 samples, was used to assess the simultaneous effect of path and parameter uncertainty on the results of the analysis (337).

Scenario analysis was used to explore how implementation may vary under different sets of circumstances. Given the set of interactions governing decision-making in the care pathway, some of which would be harder to mediate through additional investment (26), an increase in the value of supporting investments would not lead to a proportional, linear increase in improvements in outcomes (338). These interactions are therefore explored in scenario analyses.

6.3 Results

6.3.1 Disease and behaviour related factors affecting the effectiveness of TB diagnostics

After incorporating all data, assuming perfect sensitivity and specificity of health care worker decision-making around TB diagnostics, and fitting to the observed secondary outcomes, we found that the model fitted the data poorly (see Chapter 4). In order to fit the model, we needed to also consider the limitations of sputum-based TB diagnostic modalities (339). Undiagnosed TB may be related to the site of infection (extra-pulmonary TB), and low bacillary load in the sample, as is common in advanced HIV disease. During the model calibration, we therefore also added a value for the prevalence of extra-pulmonary TB (EPTB), varied along with the PPV and NPV to identify the best model fit (shown in Table 4).

6.3.2 Costs, effectiveness, and cost-utility analyses of the investment scenarios

Table 13 presents the costs, effectiveness (deaths averted and DALYs averted), and incremental cost-effectiveness ratios of investment scenarios, compared with a base case of Xpert as observed during the trial. From the provider's perspective, the incremental cost-effectiveness ratios (ICERs) ranged between \$29.12 and \$56.54 per DALY averted. We estimated a provider cost of TB services of \$89.59 (UI: \$88 - \$92) per symptomatic person tested using a Xpert-based diagnostic algorithm. The societal cost per person is estimated to be \$169.42 (UI: \$166 - \$173).

Table 13. Costs (US\$), outcomes and ICERs over three years (36 one-month cycles).

Status quo and four investment scenarios	In cohort of 10 000, true TB treated (range)	TB service costs per symptomatic individual (US\$)				Outcomes per symptomatic individual				ICERs: compared against the status quo			
		Provider costs		Societal costs		DALYs and DALYs averted		Deaths and Deaths averted		Provider cost/ DALY averted (95% UI)	Societal cost/ DALY averted (95% UI)	Provider cost/ death averted (95% UI)	Societal cost/ death averted (95% UI)
		Total (95% UI)	Incr cost (% change)	Total (95% UI)	Incr cost (% change)	Total DALYs (95% UI)	Incr DALYs averted (% change)	Total deaths (95% UI)	Incr deaths averted (% change)	(95% UI)	(95% UI)	(95% UI)	(95% UI)
Xpert (status quo)	924 (905; 942)	\$ 89.59 (88; 92)	---	\$ 169.42 (166; 173)	---	4.73 (4.6; 4.9)	---	0.13 (0.13; 0.14)	---	---	---	---	---
Xpert plus reduction in initial LTFU (iLTFU)	995	\$ 92.27	\$ 2.68	\$ 177.51	\$ 8.08	4.57	0.16	0.13	0.00	\$ 56.54	\$ 164.91	\$ 355.84	\$ 1 009.47
(C and E)	(979; 1012)	(90; 94)	3%	(174; 181)	5%	(4.4; 4.7)	3%	(0.12; 0.13)	4%	(48; 65)	(147; 183)	(287; 424)	(882; 1137)
Xpert plus treatment from negative (TfN)	1115	\$ 108.28	\$ 18.69	\$ 246.02	\$ 76.59	4.06	0.66	0.11	0.02	\$ 29.12	\$ 117.36	\$ 251.47	\$ 1 009.47
(A and E)	(1093; 1137)	(106; 110)	21%	(241; 251)	45%	(4.0; 4.2)	14%	(0.11; 0.12)	14%	(-36; 94)	(50; 184)	(125; 378)	(882; 1137)
Xpert plus improvements in the negative pathway (NP)	1404	\$ 141.07	\$ 51.49	\$ 278.24	\$ 108.82	3.44	1.29	0.09	0.04	\$ 41.82	\$ 85.84	\$ 1417.22	\$ 2 912.52
(B, D and E)	(1374; 1433)	(139; 144)	57%	(273; 283)	64%	(3.3; 3.6)	27%	(0.09; 0.10)	29%	(39; 45)	(80; 92)	(1322; 1513)	(2742; 3083)

In the Table, Incr is the incremental change in costs or effectiveness from the base case. The base case in this analysis which represents the current status quo, Xpert as observed in the intervention arm of the XTEND study; dominant: less costly and more effective; dominated: more costly and less effective; The 95% uncertainty interval (UI) is shown in parentheses; ICER: Incremental cost-effectiveness ratio; DALYs: Disability Adjusted Life Years. In the scenario column, the capital letters refer to the decision points upon which the investment scenario acts, as shown in Figure 22.

Reducing initial LTFU by starting all individuals who test positive on treatment increases the cost of treatment and patient cost of accessing care per patient (by \$2.68 and \$8.08 respectively). This scenario reduces time to starting treatment but has a comparatively small effect on the total number of people starting treatment and on health outcomes. Increasing the probability of starting treatment in month one to 100%, shifts the time-to-treatment started curve to the left, starting people on treatment who would have never started as well as those who would have started within the next couple of months. Since TB treatment does not instantly reduce the mortality rate for patients who have TB, the proportion of patients who start treatment in month one only increases by 12% in those HIV negative, 10% in those HIV negative with TB, 20% in the HIV positive group, 7% in those HIV positive with TB, 6% in those on ART, and 2% in those on ART with TB, in the reduction in iLTFU investment option.

Initiating TB treatment based on clinical signs at the follow-up visit, after a negative test result (TfN) increases the cost of TB service per symptomatic person per episode (by \$18.69), with likewise an increase in societal costs associated with accessing treatment of \$45.00 per patient, see Figure 23.

In contrast, improving access to further diagnostic tests following a negative test result (negative pathway) increases diagnostic costs by \$35 per patient due to the follow-on tests ordered, with a resultant increase in the cost of treatment (increase of \$18 per patient). This scenario disproportionately increases the patient costs associated with accessing care (from \$60 to \$105 per patient) as patients make multiple costly visits for follow-on diagnostic tests and results. In addition, delays in starting treatment increase the cost of illness due to inability to work.

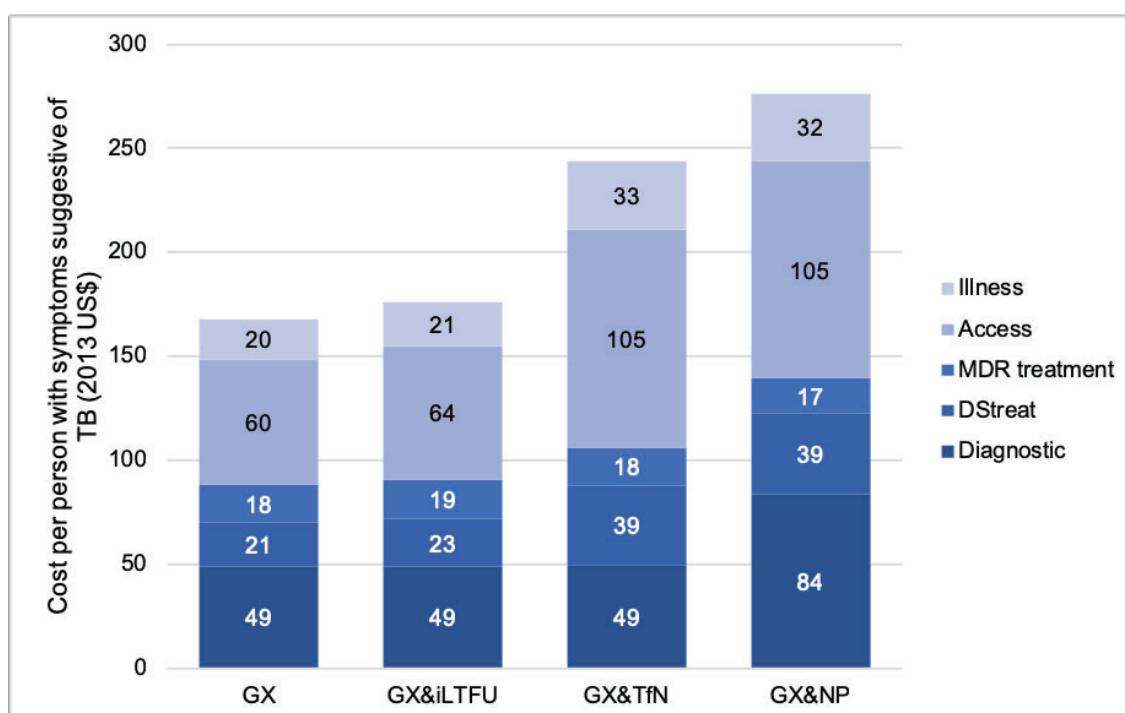


Figure 23. Societal service-level costs (US\$) per symptomatic person per episode. In the Figure; GX refers to the base option, representing the Xpert scenario; GX&iLTFU represents the Xpert scenario with investment in reducing initial loss-to-follow-up; GX&TfN represents the Xpert scenario with investment in supporting treatment from negative; and GX&NP which represents the Xpert scenario with investment in the negative pathway. The cost of accessing care (Access) includes out of pocket and time costs incurred by patients and caregivers when accessing care; the cost of illness (Illness) includes the cost of caregiver's time, the cost of patient's time when unable to work as well as loan interest, assets sold and the cost of nutritional supplements.

When comparing what happens after a negative test result between investment strategies, starting treatment after further diagnostic tests (negative pathway) is more effective than starting treatment empirically. The provider episode costs per symptomatic individual are \$108.28 (\$106 - \$110) in the treatment from negative scenario compared to \$141.07 (\$139 - \$144) in the strengthened negative pathway. Considering the societal perspective Figure 23, the cost of accessing care increases as the number of visits increases (from \$70 per person to \$137 per person in the negative pathway scenario). Likewise, longer delays in correctly diagnosing people increase the cost of illness which is based on caregiver's time as well as patient's time unable to work.

6.3.3 Investment cost and transaction cost analysis

We find that investing costs of up to \$100 per symptomatic person per transaction with the health service (see Figure 24), would not increase the ICER of these investment

scenarios to levels in excess of a cost-effectiveness threshold that reflects recent decisions adopted by the South African government (revealed willingness-to-pay) (170). For example, the decision to adopt universal ART has an estimated ICER of \$658/ DALY averted (166,319). It is therefore likely that considerable investments in strengthening supportive systems around TB diagnosis in South Africa would still be considered cost-effective.

Figure 24 reports the cost-effectiveness acceptability frontiers, which show the optimal provider investments at a range of transaction costs and cost-effectiveness thresholds. Here we considered the points at various cost-effectiveness thresholds where the optimal strategy switched at levels of transaction costs. Transaction costs refer to costs to support decision-making interactions between agents, we therefore add a transaction cost value to each decision-making interaction along the patient pathway (shown as blue dots in Figure 22). Assuming no transaction costs, investing in reducing initial loss-to-follow up was the optimal investment if the threshold was below \$30/DALY averted, but at higher thresholds, the negative pathway was the optimal investment. As the investment cost per person per transaction increased, empirical treatment became the optimal investment compared to the negative pathway at lower thresholds. This is driven by a reduction in healthcare visits when patients are started on treatment empirically.

6.3.4 Sensitivity analyses

The results of detailed univariate sensitivity analyses are shown in Chapter 7, with a summary presented here (see Figures 25). The service level costs of each intervention vary depending on the population, so for example, if much of the population is HIV-positive, the cost of the ART investment increases and so does the cost associated with the investments in what happens after a negative test result. In terms of the effect of the investments, the scenarios related to what happens after a negative test result are particularly sensitive to the prevalence of undiagnosed TB after a negative test result. Similarly, the effectiveness of these investments is also sensitive to the health-seeking behaviours of patients, specifically whether they return for their results, the availability of CXRs and whether treatment is started after further diagnostic tests. The prevalence of MDR-TB and cost of MDR-TB treatment was an important driver of costs and effectiveness of the overall results.

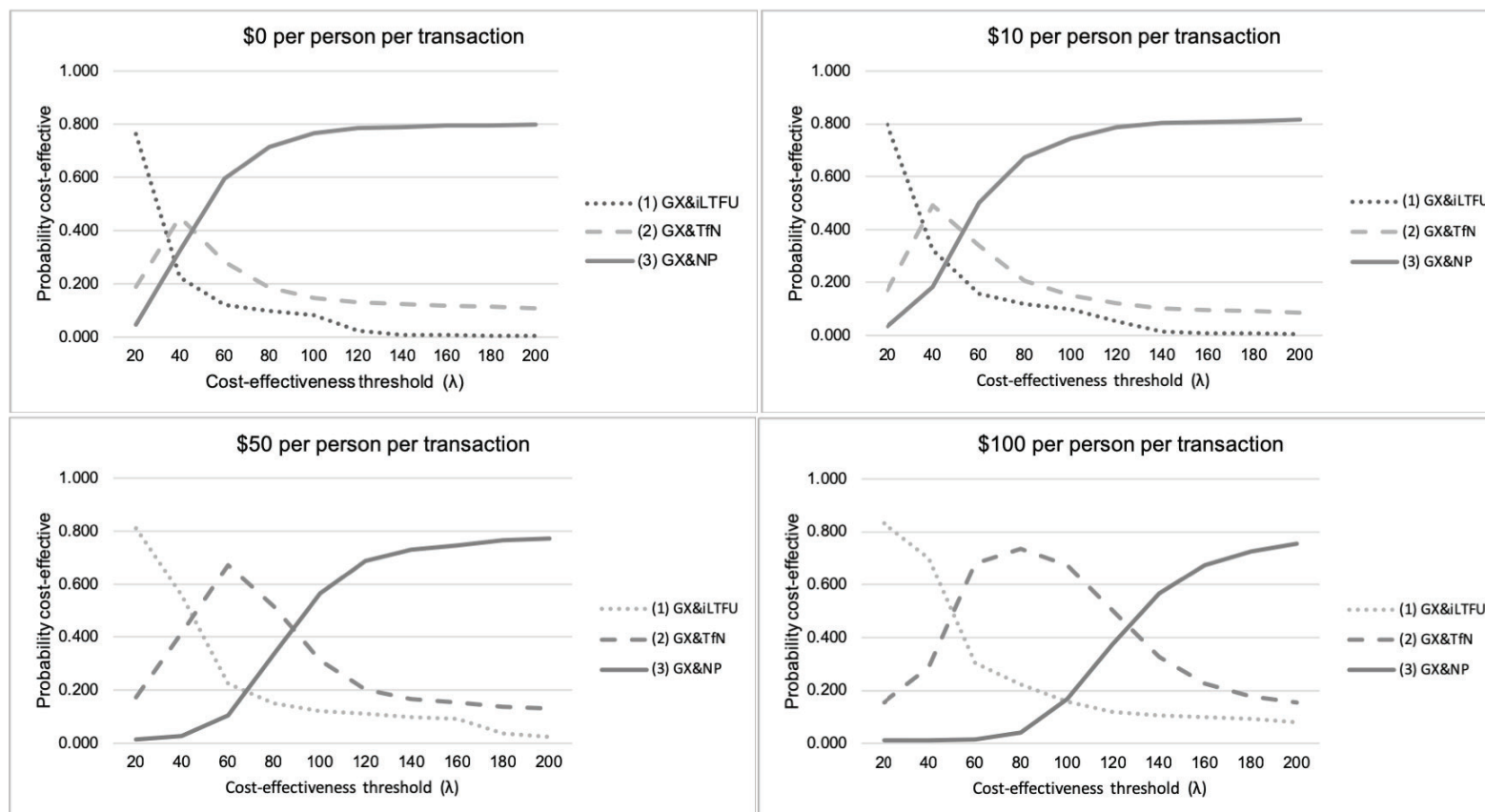
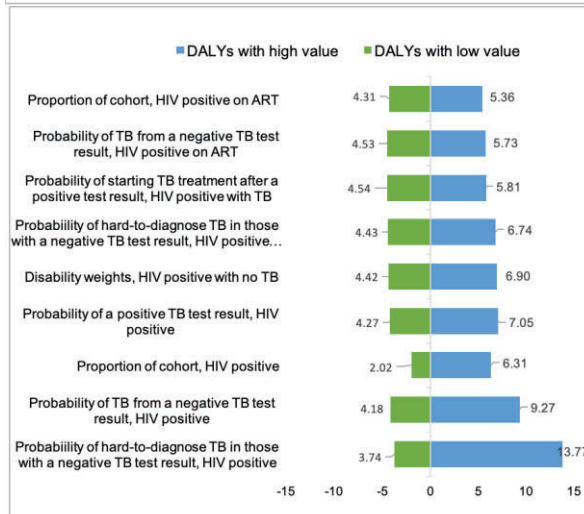
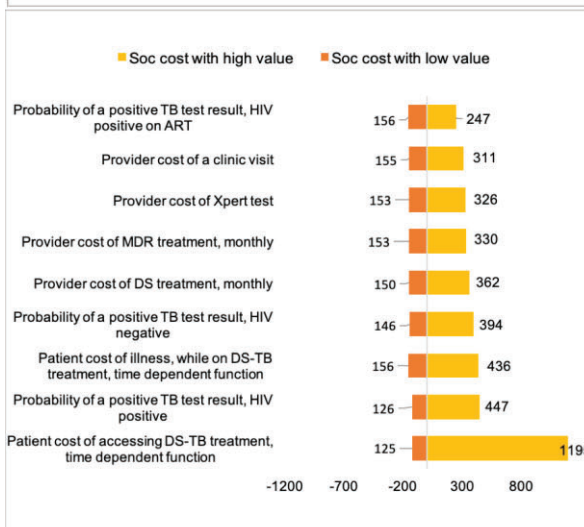
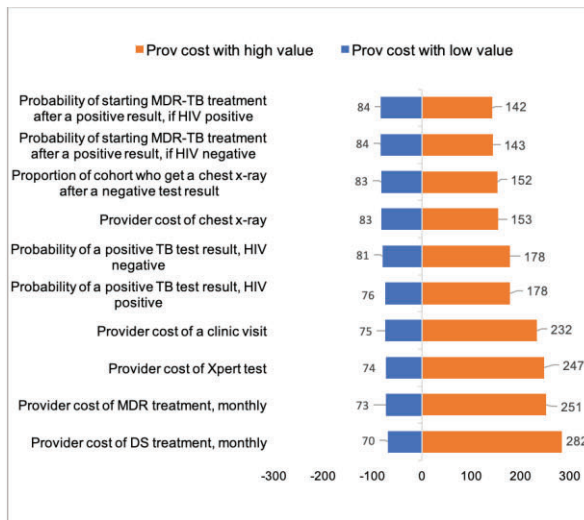


Figure 24. Provider cost-effectiveness acceptability frontiers at various levels of transaction costs.

Where iLTFU refers to the Xpert plus a reduction in initial loss to follow up scenario; TfN refers to the scenario modelling Xpert plus treatment from negative; NP refers to Xpert plus improvements in the negative pathway. The cost-effectiveness acceptability frontier (CEAF) expresses the uncertainty around the cost-effectiveness of investments, by showing which strategy is economically preferred at a range of cost-effectiveness thresholds (on the x-axis). The base case scenario for each of these comparisons is Xpert MTB/RIF use, as observed in the XTEND trial. The graph is a plot of the proportion of individual runs that would be cost-effective for each intervention (y-axis) while restricting the options to only those that would be the most cost-effective (optimal) investment for at least one individual, against a range of cost-effectiveness thresholds (x-axis). As the threshold increases, the preferred option changes, the switch point being where the incremental cost-effectiveness ratio (ICER) value increases beyond the threshold, rendering the option no longer cost-effective (340). The analysis is repeated at a range of transaction costs per person, thereby varying the costs needed to be invested to facilitate systems level change in line with the investment strategy.



Figures 25(A), 20(B) and 20(C): Results from the univariate sensitivity analyses, showing the ten parameters with the greatest influence on the (A) provider cost, (B) the societal costs, and the (C) effectiveness (DALYs) of the base case. The full results for these analyses are presented in Table 15. In each one-way analysis, one parameter was varied by a factor of $10^{\dagger\dagger}$ from the mean to produce the low and high estimates, with all other variables kept constant at their respective means. Where DALYs are disability

$\dagger\dagger$ The values of each of the variables was multiplied by 10 to produce the high value and divided by 10 to produce the low value.

adjusted life years; Prov standard for provider; and Soc is societal. DS treatment is drug-sensitive treatment. MDR is multi-drug resistant.

6.4 Discussion

Our analyses build on a global body of work that has evaluated the use of Xpert-based diagnostic guidelines (221,226,233,235,247,341,342), by presenting the costs, effectiveness, and cost-utility of complementary investments to strengthen the diagnostic pathway and by considering how these investments may interact with the costs incurred by patients (79). We explored how investments along the patient pathway and the strengthening of health systems may affect the impact and resource use associated with TB diagnostics. The results of our analysis suggest that it is unlikely that a single investment or technology would dramatically improve the outcomes for symptomatic patients receiving a TB diagnostic test; instead our results suggest that investments in various parts of the care pathway could generate additional benefits, and, based on the transaction cost analysis, we show that relatively high levels of investment in health systems strengthening would be cost-effective. When comparing across the care pathway (see Table 2), our analysis finds that in a symptomatic cohort with 13% prevalence of TB, only minor reductions in mortality can be achieved by improving initial pre-treatment loss to follow up, while much larger benefits can be achieved by improving access to further tests after a negative TB test (the negative pathway). This may be explained, in part, by the higher mortality rates observed in people who are HIV positive with an initial negative TB test result.

6.4.1 Potential drivers of investment value

While the Xpert assay automates diagnostic processes, with results (TB & MDR-TB) generated within two hours and could potentially be used to facilitate same-day diagnosis, machines were placed at laboratories in South Africa, with results delivered to health facilities within two days. At these laboratories, Xpert implementation sparked efforts to reduce the turnaround time of results, nevertheless a follow-up clinic visit by patients was still required (165). While the need to improve the linkage of patients with their results has been highlighted as an important component of better TB diagnosis, our analysis suggests that low gains in terms of mortality reduction would be achieved in such an

investment scenario (relative to the other scenarios modelled). This may be driven by lower mortality rates in those with positive sputum test results, given that people living with HIV who have high rates of TB-associated mortality are less likely to have a positive sputum test result. While the mortality reduction is likely to be modest, those with positive TB test results are potentially transmitting TB disease in communities, increasing the future burden of need at a population level (343). These results are somewhat supported by findings from recent studies that highlighted the challenges of point-of-care (POC) Xpert testing at facilities in urban settings (344) but also the benefits in a rural community (345).

Clinical decision making (empiric TB treatment) after a negative test result has been shown to be important in understanding the cost-effectiveness of new TB diagnostics and that greater awareness of TB symptoms among health care workers may improve outcomes and be a cost-effective intervention (14,233,346). In Uganda, Hermans et al. (2017) found that TB treatment was initiated based on clinical symptoms in 18% of patients (333). In Cape Town, South Africa, an evaluation of TB programmatic data found that, following the introduction of Xpert, there was a decline in the use of empirical TB treatment from 42% to 27% (334). It is possible that the introduction of Xpert did not significantly reduce TB-associated mortality due, in part, to a reduction in action, including follow-on tests, after a negative test result (332). However, access to further tests after a negative result (CXR and culture) is dependent on both the availability of tests in close proximity to the health facility as well as how the affordability of additional visits to patients influences health seeking behaviour (81,104,309). Our analysis suggests that assumptions of how quickly TB treatment reduces mortality rates are determinants of the effectiveness of this strategy.

6.4.2 Investing in health systems strengthening

While it is not possible to say whether an investment scenario is cost-effective without consensus on a cost-effectiveness threshold in South Africa, we find that investing in strengthening health systems to support the TB diagnostic algorithm is likely to be a high value investment. The outcomes of these investments are also likely to influence other disease programs and sectors (32). We do not include these spill-over benefits in our analysis, and thus our estimates are conservative. Recent empirical work has highlighted

the importance of going beyond investing in assets and technology to also invest in developing agency and governance in health systems (347). Those investments are highly contextual and difficult to cost, so while our approach highlights to decision makers the resource envelopes required, more work is needed to develop and iteratively assess context-specific investment strategies.

The following limitations should be considered when interpreting our findings. Firstly, we did not model the effect of the various scenarios on the TB epidemic at a population level. While the implementation of Xpert primarily resulted in an increased identification of smear-negative TB, currently thought not to be a major driver of transmission, not including transmission in the analysis is likely to discount the comparative benefit of reducing pre-treatment LTFU at a population level (343,348,349). Secondly, while we are modelling scenarios and benefits in a nuanced way, the relationship between health system structures and health care worker and patient/ community behaviour is highly complex and while one can observe patterns, predictions will be limited by our understanding of the mechanisms driving these patterns. It is also possible that the reason for the existence of this gap in practice are due to structural challenges in the system that may be harder to mediate than our analysis suggests. Thirdly, any investment in the health system will be likely to have an impact on other associated services, the benefits of which we did not include in our analysis (165). And lastly, while our model includes a pathway for patients to initiate drug-resistant TB treatment if diagnosed, and individuals will initiate DR-TB treatment and incur the associated costs, we do not attempt to estimate the true prevalence of DR-TB or what effect the investments may have on the DR-TB epidemic. In the analysis of the negative pathway therefore, the model may be underestimating the effect of incorrectly starting an individual on drug-sensitive TB treatment and continued transmission of DR-TB. It should be noted though that following the roll-out of Xpert, studies have found that barriers to initiating DR-TB persisted and that the time to correct treatment was only slightly reduced (75,306).

6.5 Conclusion

In summary, our findings suggest that within the context of a high TB prevalence setting, with a well-developed laboratory infrastructure, it is important that the implementation of a TB diagnostic test is accompanied by additional investments. Investments in the health system to support TB diagnosis of approximately \$100 per patient per interaction with the health system may still be considered highly cost-effective. Our analysis also suggests that there is a high prevalence of undiagnosed TB in those who are symptomatic (passive case finding) in South Africa. South African policy and elsewhere is to substantially expand and intensify case detection, yet if this is not supported with substantial investments in the health system, it may place further burden on a health system that is struggling to implement passive case detection, and the impact of these policies may also be modified. Focussing effort on ensuring quality along the patient pathway therefore remains critical if the large investments in TB diagnostics are to achieve their potential.

Additional figures

At lower levels of transaction costs, strategies have a higher probability of being cost-effective at lower CET.

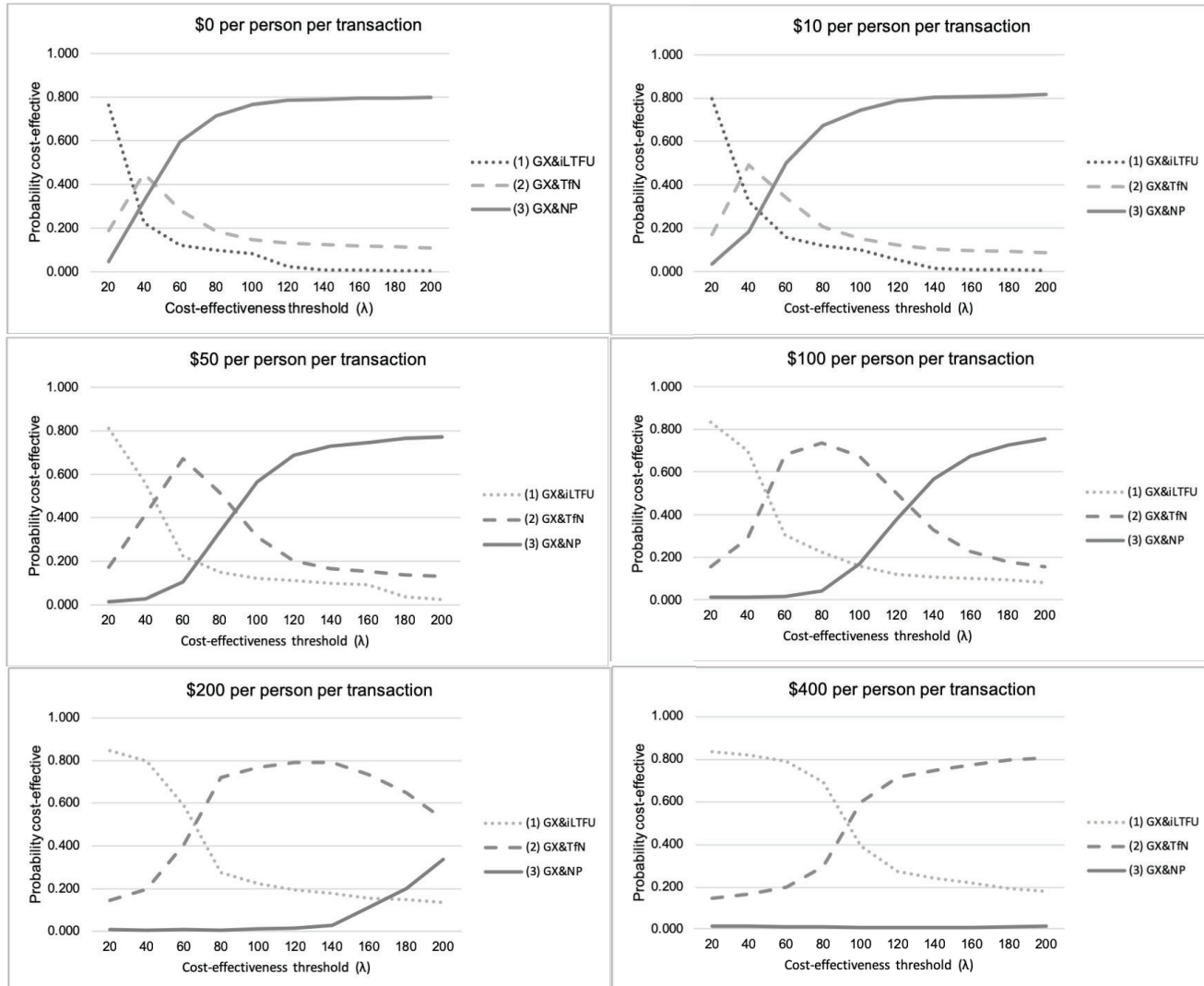


Figure 26: cost-effectiveness acceptability curves at various levels of transaction costs

CHAPTER 7: BEHAVIOUR AND DECISION-MAKING

Summary

In this chapter, the theoretical literature introduced in Chapter 3 are used to interpret the results of additional scenario and sensitivity analyses conducted using the model shown in Chapter 6, identifying possible policy leverage points and exploring how the behaviour of agents will mediate the cost-effectiveness of investments in technology. The results are interpreted and discussed with reference to the theoretical literature and the implications for decision-making are outlined. In the model, the behaviour of healthcare workers is explored in three distinct ways 1) by using data from a pragmatic trial reflecting routine practice and clinical decision-making at the time of the study; 2) by developing a conceptual framework of the relationships between behaviour at decision points and disease outcomes; and 3) by investigating how these interactions may influence the value of the diagnostic algorithm. In this chapter, the analytic focus is on the third point. The chapter is concluded by reflecting on approaches to incorporating health systems interactions in economic evaluation models.

7.1 Introduction

The diagnosis of TB is dependent not only on the diagnostic test, but also on both the context as well as the behaviour of health care workers who implement the test (219,222,350). During the implementation of Xpert, it was found that health care workers were less likely to request additional diagnostic tests for patients following a negative TB test result than if the initial test was a sputum smear microscopy (271,272). It was thought that healthcare workers had overestimated the ability of Xpert to identify all TB, while people knew the limitations of microscopy and therefore requested additional tests if they continued to suspect TB infections. However, these differences in practice were also affected by the availability of chest x-rays as additional diagnostic tests, as well as patients' continued symptoms at follow-up visits (272). These differences between what the expected and the observed movement of patients through the care pathway, was attributed to health systems weaknesses. The analysis presented in Chapter 6, found that

investments in supporting TB diagnosis would be considered high value investments, but the decision would vary depending on the context of implementation. Cost-effectiveness analyses are commonly used to provide guidance to national – or global level decision-makers on how best to spend scarce resources in order to maximise the benefit gained. However, in decentralised health systems, especially in low- and middle income country (LMIC) settings where there is no central body making purchases, and therefore decisions on resource spending that guides clinical practice are often made at a local level, yet economic evaluations tend to not provide enough guidance on which decision would be most appropriate given a specific context (16). In considering health systems in economic evaluations, questions that have been raised in extending the use of economic evaluation has included whether payers should invest in health systems or in technology (351) and explored how to include the interactions with systems (46,245), but there has been less guidance on how to present local level policy makers with nuanced advice on the implication of one decision over another. Diagnostic processes are highly dependent on the behaviour of those who use the guidelines in routine practice; for the interpretation of test results, deciding who should be tested, and following up to ensure that treatment is completed, and is therefore a good example to explore key challenges with these analyses.

7.2 Methodology

The model, developed in Chapter 4, with the results discussed in Chapter 6, was used to first conduct univariate sensitivity analyses to understand how variation in individual model parameters would influence the decision. These interactions were classified based on whether they related to structure, behaviour or biological processes. Secondly, scenario analyses were developed to explore how implementation in specified contexts would change the optimal decision.

In the univariate sensitivity analyses, every model parameter was varied by a factor of 10 and the outcomes are presented in the Table below. The main drivers of the provider costs were the cost of treatment (particular MDR TB treatment), the cost of clinic visits as well as the costs of chest x-rays. If the proportion of the population that was HIV positive was

higher – this was also a key factor in higher provider costs. Proportion of the cohort, HIV positive as well as the proportion of patients with hard-to-diagnose TB were also key drivers of the outcomes of the model.

Decision points in the TB diagnostic pathway were identified, along with the downstream decision points that they in turn will influence, based on the conceptual framework of the model. These decision points are places in the pathway where health care workers and patients have an interaction, or where alternative courses of action that influence TB outcomes (particularly mortality) occur. These were identified based on a combination of the clinical guidelines used in health facilities, the movement through care captured in the pragmatic cluster randomised control study, and an understanding of the range factors that influences these decisions based on the observations done by the researchers while collecting data for the primary cost analyses (198,257,331). We explore how alternative patterns of behaviour will affect the value of the TB diagnostic algorithm in South Africa by varying multiple interacting probabilities in the pathway.(198,257,331). The results of these analyses are presented in Table 14.

7.2.1 Analytical framework

There is no unifying definition of what constitutes investments in strengthening health systems. Some have conceptualised health systems investments in terms of changing the structure of the health system, by investing in additional technology, trained healthcare workers or additional budget to improve the service more broadly (88). As discussed in Vassall et al., these investments are crucial to support the implementation of new technologies in the longer term and are important for planning resource needs to support the sustainable implementation of new technologies (28). For example, improved diagnostic technologies are likely to increase the number of patients to be started on treatment or will require additional human resource time to identify those in need of a test. Under the assumption that health systems are functioning at maximum capacity, additional investment in human resources will be needed to support the implementation of the revised diagnostic guidelines.

Analytical approaches evaluating systems wide investments required, have the potential to allow us to identify the additional resources required for budgeting purposes, and are

therefore important predictive tools to assist policy makers. However, may have less explanatory ability – to assist in an understanding of why and how the outcomes of an investment differ from what was intended, to explore contextual heterogeneity and to provide more realistic estimates of cost-effectiveness, with the aim of identifying possible policy leverage points. This approach can be extended, by conceptualising and then modelling the relationship between health system investment and health outcomes (as presented in the model conceptual framework). Building on conceptual frameworks proposed by Aragon (318) and Hanson et al. (91), we conceptualise the interaction with the patient (see Figure 27) as one that is shaped by the structure of the health system, the use of structure through the formal and informal rules of the system (including clinical guidelines), as interpreted by healthcare workers and expressed through clinical decision-making. Figure 27 below summarises the relationships identified between these interactions.

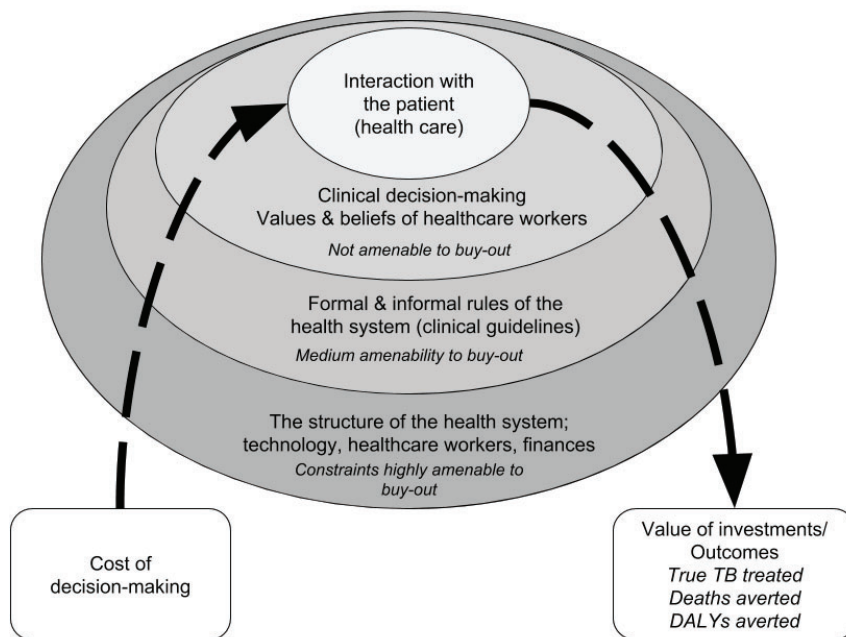


Figure 27. Analytical framework for exploring the implementation of health systems strengthening investments developed based on the literature reviewed. In the Figure, DALYs refers to disability adjusted life years.

7.2.2 Scenario analyses

Rather than variability in a single variable, the particular characteristics and patterns of the system within which an investment is implemented, is represented by changes in multiple variables simultaneously.

Initial loss-to-follow up refers to the number of patients, who have a positive TB diagnostic test but is not started on treatment within one month of the diagnostic test. This statistic is collected routinely for TB services, and this is reported in **Error! Reference source not found.** This is often used as indicator of the quality of TB services provided. However, within a clinic environment, the pathway of patients through the clinic means that in order to reduce initial loss-to-follow-up, patients need to be started on treatment at the point of diagnosis. Some of the challenges that arise

1. In the initial LTFU scenario, we varied the probability of starting treatment after a positive test result between 25% to 100%.
2. Lower the mortality reduction due to TB treatment started in those who have TB to 0.005 in HIV positive patients and 0.001 in patients on ART.
3. Changed the characteristics of the population so that the entire HIV positive population is on ART.
4. Used the highest RR-TB diagnosis reported by Naidoo et al. 4.6% (3.5 – 5.7), implemented after positive, negative and out of care – a significant increase from XTEND where 1.9% and 2.5% was diagnosed with drug-resistant TB.
5. Greater access to the negative pathway, with 70% of those eligible gets the negative pathway and 80% of those with TB starts treatment.
6. Models settings with low patient return rates to the clinic, such as possibly more rural clinics or where there is a lot of migration
7. Increased prevalence of extra-pulmonary TB, hard to diagnose using a sputum-based diagnostic test but may be diagnosed using chest x-rays

7.3 Results

Table 15 shows the results of the univariate sensitivity analyses. Each variable was varied individually and the effect of that variation on the provider costs, societal costs and effectiveness of the base case was estimated. Considering the impact on provider costs, costs related to the structure of the health system were the largest determinants in variation in costs. These included (with percentage variation shown in brackets), the costs drug-sensitive treatment (26%), MDR treatment (18%), Xpert test (17%), clinic visit (14%) and chest x-ray (3%). Disease specific factors including the prevalence of TB contributed approximately 6% to variation. And factors related to the behaviour of healthcare workers contributing to variation in costs included whether a chest x-ray was ordered from a negative initial test result (3%).

Considering the effect of changing variables on the effectiveness of the baseline result, disease specific factors have the greatest impact on variability. The prevalence of extra-pulmonary TB has the greatest impact on outcomes, contributing 59% and the proportion of the population who is HIV positive, contributes 11%, followed by the prevalence of bacteriologically confirmed TB at 5%. Behavioural variables contribute less, with the probability of starting treatment only contributing 1%.

Univariate analysis is however likely to underestimate the impact that behaviour is likely to have, as behaviour on more than one variable in a chain needs to be modified to improve an outcome. For example, increasing the proportion of patients initiating the negative pathway, will not a substantial effect on outcomes unless the proportion of patients who start treatment correctly from the negative pathway, is also increased. Additional multi-variate analyses were therefore conducted to understand how different contexts are likely to change the prioritisation of the optimal investment strategy.

Table 14. Multi-variate sensitivity analyses.

Scenario	GX&iLTFU	GX&TfN	GX&NP	Change in prioritisation	Comments
	ICER (2013US\$)	ICER (2013US\$)	ICER (2013US\$)		
Primary estimate	51.42	117.83	84.07		
Initial loss to follow up, high (25%)	45.44	116.27	83.29		ptxfpos changed to (1-0.25)
Reducing mortality from treatment started	45.64	102.07	72.74		tMort_treat_i1 = 0.005; tMort_treat_i2 = 0.005; and tMort_treat_i3 = 0.001
Universal ART (100% of HIV positive cohort is on ART)	N/A	159.75	85.23	***	This gives the same change in ICER as was observed in the iLTFU option; change here is not attributable to ART but to reducing ILTFU - fix this.
Percentage of patients who start MDR-TB treatment	77.81	241.86	82.20		used the highest RR-TB diagnosis reported by Naidoo et al. 4.6% (3.5 - 5.7), implemented after pos neg and ooc, an increase from XTEND between 1.9% and 2.5%. XTEND underpowered for this.
Greater access to the negative pathway; 70% of those eligible gets the negative pathway and 80% of those with TB starts treatment.	51.49	662.43	110.88		
Low patient return rate for a second visit (10xbase)	63.33	155.16	446.67	***	In settings with low return rate; only 10% of people return at each decision point
High pEPTB, increased to 30% in those HIV positive, and those on ART	51.49	61.51	45.89	***	

In the Table, for each scenario the block that corresponds to the optimal investment has the darkest colour, with the colour then decreasing in intensity to the least cost-effective option. In the last column of the table, three stars are used next to the scenarios where the optimal strategy for investment differs from the one presented for the primary estimate. Where pEPTB refers to the probability of extra-pulmonary TB; MDR-TB is multi-drug resistant TB; GX&iLTFU refers to the scenario where the investment is to reduce initial loss-to-follow-up; GX&TfN is the scenario with treatment from negative; and GX&NP is the investment with support for further diagnostic tests in the negative pathway.

In settings with high initial loss to follow-up, such as what has been observed in the Western Cape of South Africa, investment in reducing initial loss to follow-up continues to be the best value intervention, if we do not consider the additional costs to find those remaining patients. Another scenario that leads to a change in the prioritisation of investments is if there is a higher prevalence of MDR-TB in the initial cohort, with investments in the negative pathway becoming more cost-effective relative to other options. If we assume that in some contexts, patients will have a lower rate of return to care, we find that investment options that reduces the number of visits by starting patients with TB on care sooner becomes more cost-effective. In settings with higher prevalence of Extra-pulmonary TB, investing in the negative pathway of starting empirical treatment (352) becomes the optimal solution to be prioritised.

7.4 Discussion

7.4.1 Policy levers for supporting TB diagnosis

The analyses presented above shows how the interactions between disease (such as the prevalence of hard-to-diagnose TB, or the limitation of sputum-based diagnostic tests), as well the behaviour of healthcare workers through the reduced probabilities of routine care and access to certain diagnostic tests interact, and dictates the value of the implementation of a new diagnostic in routine care settings.

Key policy levers identified above, include strategies to encourage healthcare workers to facilitate further testing for TB (the negative pathway). Our results however show that access to the tests alone is unlikely to be sufficient in reducing mortality, it is crucial to also ensure that treatment is started after further diagnostic tests. These results are supported work conducted by Fairall et al. who found that working with healthcare workers to increase their awareness of TB and the procedures for testing for TB, was a highly cost-effective investment (14).

As was argued by Hanson et al., evaluating investments to strengthen the health system to improve specific health outcomes in the health system requires an understanding of constraints in the system. A challenge in investigating constraints, is that not all constraints will act in the same way. Some constraints will be more amenable to investment than others.

7.4.2 Amenability to buy out

The behaviour of agents acting under uncertainty, can be expressed as a function based on a set of interactions, as presented in the conceptual framework (see Figure 7). These functions, sometimes called utility functions in economics, are analogous to the concept of fitness costs in ecology (22: 41, 143). In neoclassical economic theory, the utility function of an individual is an expression of the behaviour of agents attempting to maximise their individual utility within a budget or set of resource constraints (353). The utility functions estimated express the behaviour of health care workers as the agents,

responding to a set of contextual interactions which includes the prevalence of the disease, the types of disease observed (the prevalence of extra-pulmonary TB), the behaviour of patients, a response to a set of institutional rules or norms (expressed as diagnostic and treatment guidelines) as well as a response to a set of resource constraints (116). Given that this model expresses the average behaviour of a set of agents (a cohort) as opposed to the actions and outcomes of individuals, the dynamic utility function is an expression of the average behaviour of health care workers under a set of circumstances, with heterogeneity of behaviour expressed in the uncertainty estimates.

We identified four primary interaction points where decisions are to be made by healthcare workers. These include the decision to start TB treatment after a positive TB test result (C). These decisions will also influence other interactions with patients, for example if more tests are ordered after an initial negative test result, a follow-on decision that will influence outcomes is whether TB treatment is started after follow-on tests (D). Similarly, where no further action was taken within a one-month period, patients would move to an out-of-care state with a probability of starting treatment from out-of-care (E). Each of the utility functions are also influenced by the prevalence of TB within the cohort.

The decision after a negative initial TB test result is constructed as two interacting decisions, starting treatment without further evidence (P_A) and ordering additional diagnostic tests (P_B). These decision utility functions can be conceptualised as a function of patients returning to care for follow-up visits; the prevalence of symptoms after a negative test result and the sensitivity of the WHO symptom screen as implemented in health facilities; as well as an access variable used to explore how constraints in terms of access to TB treatment or to further diagnostic tests may influence the results of the study.

$$P_A = r_{i,t} (s_{i,t} \cdot w_i)^\alpha \alpha_A \quad (3)$$

Where P_A is the probability of starting TB treatment after an initial negative test result and without further diagnostic tests; r is the probability that the patient will either return for a follow-up visit (demand-side) or will be followed up by health care workers including community health workers in the community (supply-side); s is the diminishing probability of TB-associated symptoms at subsequent visits to the health facility (modelled as a Poisson regression); w represents the sensitivity of the WHO symptom screen tool when implemented at a routine facility; and α_A as an access variable.

This utility function assumes that this decision can only be taken at the next visit of the patient at a healthcare facility, that action can only be taken at the visit when the patient returns to the clinic for results.

$$P_B = r_{i,t}(s_{i,t} \cdot w_i)^\alpha a_B \quad (4)$$

Where P_B is the probability of ordering additional diagnostic tests thus initiating the negative pathway after an initial negative TB test; r is the probability that the patient will either return for a follow-up visit (demand-side) or will be followed up by health care workers including community health workers in the community (supply-side); s is the diminishing probability of TB-associated symptoms at subsequent visits to the health facility (modelled as a Poisson regression); w represents the sensitivity of the WHO symptom screen tool when implemented at a routine facility; and α_B as an access variable. Representing the proportion of facilities that will have access to chest x-rays.

Each of the utility functions influences the proportion of the cohort in a specific state and thus influences upstream decisions, including the decision to start treatment from out of care and starting treatment after further tests following a negative TB test result.

Where interactions are largely driven by the behaviour of healthcare workers in the system, there is some potential for incentivising the behaviour of agents to improve TB outcomes. The transaction costs analyses shown in Chapter 6 suggests that investing in incentivising these transactions is likely to be highly cost-effective. However, as was shown in the sensitivity analyses, many of these interactions are driven by the characteristics of TB and the limitation of sputum-based diagnostic modalities. These constraints could only be bought-out through the development of new diagnostic modalities (223,354)

7.5 Conclusion

Economic evaluations based on extra-welfarist theory values health outcomes (often mortality outcomes). However, for health systems, an investment that improves processes within the health system may add greater value to related systems processes (159: 81). For example, investing in additional x-ray facilities will have a benefit in terms of a health outcome attached to improved TB services. However, the reorganisation of health services in order to implement the x-ray facility may strengthen processes in the health system, in ways that would also improve patient outcomes or reduce patient costs.

Beyond the valuation of outcomes related to health or processes, time preference as used in economic evaluation may also unfairly weight investment options against health systems strengthening. When evaluating a clinical or public health investment, investment costs required to set to strengthen systems, may due to the nature of the disease only have an impact on epidemic control or disease outcomes at a time point beyond the evaluation period of the trial.

A third challenge in conducting economic evaluation of health systems investments, is that within decentralised health systems, it is possible that some of the costs of implementing a system strengthening intervention would fall on another budget – with implication for considering optimisation of health outcomes against the healthcare budget (32).

In this section, challenges and approaches to evaluating health systems investments in economic evaluations are outlined. These include:

- Valuation of health or process
- Time preference
- Falls on different budgets, leading to difficulties in defining the threshold
- Modelling complex interactions, by observing patterns and those changes the behaviour of agents.

Additional tables

Univariate sensitivity analyses

Univariate sensitivity analyses were conducted whereby every model parameter was varied by a factor of 10^{vii} and the outcomes are presented in the Table below. The main drivers of the provider costs were the cost of treatment (particular MDR TB treatment), the cost of clinic visits as well as the costs of chest x-rays. If the proportion of the population that was HIV positive was higher – this was also a key factor in higher provider costs. Proportion of the cohort, HIV positive as well as the proportion of patients with hard-to-diagnose TB were also key drivers of the outcomes of the model.

Table 15. Univariate sensitivity analysis, varying each variable in the model and recording change in effectiveness, provider – and societal costs.

Parameter description	Provider perspective (Base: \$89.37)			Societal perspective (Base: \$168.80)			Effectiveness (Base: 4.64 DALYs)				
	Low value	High value	Cost_low value	Cost_high value	% var	Cost_low value	Cost_high value	% var	DALYs_low value	DALYs_high value	% var
Provider cost of DS treatment, monthly	3	309	70	282	26%	150	362	3%	4.64	4.64	0%
Provider cost of MDR treatment, monthly	52	5168	73	251	18%	153	330	2%	4.64	4.64	0%
Provider cost of Xpert test	2	169	74	247	17%	153	326	2%	4.64	4.64	0%
Provider cost of a clinic visit	1	86	75	232	14%	155	311	2%	4.64	4.64	0%
Prob of a positive TB test result, HIV positive	0	1	76	178	6%	126	447	7%	4.27	7.05	5%
Prob of a positive TB test result, HIV negative	0	1	81	178	5%	146	394	4%	4.62	4.89	0%
Provider cost of chest x-ray	2	152	83	153	3%	162	233	0%	4.64	4.64	0%
Prop of cohort who get a chest x-ray after a negative test result	0	5	83	152	3%	163	232	0%	4.64	4.64	0%
Prob of starting MDR-TB treatment after a positive result, if HIV negative	0	0	84	143	2%	161	246	0%	4.64	4.65	0%
Prob of starting MDR-TB treatment after a positive result, if HIV positive	0	0	84	142	2%	162	242	0%	4.63	4.76	0%
Provider cost of a LPA test	2	203	85	133	1%	164	213	0%	4.64	4.64	0%
Prob of starting MDR-TB treatment from out-of-care, if HIV positive on ART	0	1	84	117	1%	162	209	0%	4.64	4.64	0%

^{vii} The value of each parameter was multiplied by ten to get the input parameter for the high value; and divided by ten to get the input parameter for the low value.

Prop of cohort who access a clinic after a negative test result, if HIV positive	0	7	87	115	0%	166	194	0%	4.64	4.64	0%
Prob of starting MDR-TB treatment after positive result, if HIV positive on ART	0	0	89	115	0%	169	206	0%	4.64	4.65	0%
Prop of cohort who get a DST for Rif resistance after a negative result	0	1	87	108	0%	167	188	0%	4.64	4.64	0%
Provider cost of a hospital bed day	7	716	88	106	0%	167	185	0%	4.64	4.64	0%
Prop of cohort who access a clinic after a negative test result, if HIV negative	0	7	88	105	0%	167	184	0%	4.64	4.64	0%
Prob of a positive TB test result, HIV positive on ART	0	1	87	104	0%	156	247	1%	4.50	4.66	0%
Prob of starting MDR-TB treatment from out-of-care, if HIV positive	0	0	89	106	0%	169	192	0%	4.64	4.65	0%
Prop of cohort, HIV positive on ART	0	0	84	100	0%	158	193	0%	4.31	5.36	1%
Prob of starting TB treatment after a positive test result, HIV positive with TB	0	1	76	91	0%	128	173	0%	4.54	5.81	1%
Prop of cohort who get a DST for INH resistance after a negative test result	0	1	88	102	0%	168	181	0%	4.64	4.64	0%
Provider cost of a smear microscopy test, fluoro-microscopy	1	63	88	101	0%	168	181	0%	4.64	4.64	0%
Provider cost of a culture test	1	129	88	100	0%	168	180	0%	4.64	4.64	0%
Prop of cohort who get a smear microscopy test after a negative test result	0	2	88	100	0%	168	179	0%	4.64	4.64	0%
Prop of cohort who access a clinic after a negative test result, if HIV positive ART	0	10	88	99	0%	168	179	0%	4.64	4.64	0%
Prop of cohort hospitalised after a positive test result, HIV positive	0	2	89	99	0%	168	178	0%	4.64	4.64	0%
Prop of cohort who access a clinic after a positive test result, HIV positive	0	16	88	98	0%	168	178	0%	4.64	4.64	0%
Prop of cohort who get a culture test after negative test result	0	1	89	97	0%	168	177	0%	4.64	4.64	0%
Prob of starting TB treatment after a positive test result, HIV negative with TB	0	1	82	89	0%	149	168	0%	4.65	4.89	0%
Prop of cohort hospitalised after a negative test result, HIV positive on ART	0	1	89	95	0%	168	175	0%	4.64	4.64	0%
Prob of starting the negative pathway after a negative test result, HIV positive	0	0	89	95	0%	168	174	0%	4.64	4.64	0%
Prop of cohort hospitalised after a negative test result, HIV positive	0	0	89	94	0%	168	174	0%	4.64	4.64	0%
Prop of cohort who get a DST for Rif resistance after a positive test result	0	2	89	93	0%	168	173	0%	4.64	4.64	0%
Prop of cohort who get a second Xpert test as part of the negative pathway	0	9	89	93	0%	168	173	0%	4.64	4.64	0%
Prob of TB from a positive test result, HIV positive	0	1	85	89	0%	165	169	0%	3.95	4.65	0%
Prop of cohort who get a DST for INH resistance as part of the negative pathway	0	7	89	93	0%	168	172	0%	4.64	4.64	0%

Prop of cohort who get a DST for Rif resistance as part of the negative pathway	0	7	89	93	0%	168	172	0%	4.64	4.64	0%
Prop of cohort hospitalised after a positive test result, HIV negative	0	2	89	93	0%	169	172	0%	4.64	4.64	0%
Prop of cohort hospitalised after a positive test result, HIV positive on ART	0	2	89	92	0%	169	172	0%	4.64	4.64	0%
Prop of cohort hospitalised as part of the negative pathway, HIV positive	0	2	89	92	0%	169	172	0%	4.64	4.64	0%
Prob of starting TB treatment after a positive test result, HIV positive with TB	0	1	87	89	0%	157	169	0%	4.63	5.03	0%
Prop of cohort who get a culture test as part of the negative pathway	0	7	89	92	0%	169	171	0%	4.64	4.64	0%
Prob of starting treatment from the negative pathway, HIV positive no TB	0	1	89	92	0%	169	179	0%	4.61	4.64	0%
Prop of cohort who access a clinic after a positive test result, HIV negative	0	11	89	91	0%	169	171	0%	4.64	4.64	0%
Probability of starting treatment after a negative test result, HIV positive	0	0	89	91	0%	168	177	0%	4.62	4.64	0%
Prob of starting the negative pathway after a negative test result, HIV positive ART	0	1	89	91	0%	169	171	0%	4.64	4.64	0%
Prop of cohort, HIV positive	0	1	88	90	0%	157	176	0%	2.02	6.31	11%
Prop of cohort who get a DST for INH resistance after a positive test result	0	1	89	91	0%	169	171	0%	4.64	4.64	0%
Prop of cohort who get a smear microscopy test after a positive test result	0	3	89	91	0%	169	171	0%	4.64	4.64	0%
Prop of cohort who access a clinic after a positive test result, HIV positive on ART	0	11	89	91	0%	169	171	0%	4.64	4.64	0%
Prop of cohort starting MDR-TB treatment after negative test result, HIV positive	0	0	89	91	0%	169	171	0%	4.64	4.64	0%
Prop of cohort who get a chest x-ray as part of the negative pathway	0	4	89	91	0%	169	171	0%	4.64	4.64	0%
Provider cost of an antibiotic trial	0	3	89	91	0%	169	170	0%	4.64	4.64	0%
Prop of cohort hospitalised after a negative test result, HIV negative	0	0	89	91	0%	169	170	0%	4.64	4.64	0%
Prop of cohort who get an antibiotic trial after a negative test result	0	6	89	91	0%	169	170	0%	4.64	4.64	0%
Prop of cohort hospitalised as part of the negative pathway, HIV positive on ART	0	2	89	91	0%	169	170	0%	4.64	4.64	0%
Prop of cohort who get a chest x-ray after a positive test result	0	1	89	90	0%	169	170	0%	4.64	4.64	0%
Prob of starting TB treatment after a positive test result, HIV negative	0	1	88	89	0%	166	169	0%	4.64	4.64	0%
Prop of cohort who get a second Xpert test after a positive test result	0	1	89	90	0%	169	170	0%	4.64	4.64	0%

Prop of cohort who access a clinic as part of the negative pathway, HIV positive	0	6	89	90	0%	169	170	0%	4.64	4.64	0%
Prob of starting the negative pathway after a negative test result, HIV positive with TB	0	0	89	90	0%	169	171	0%	4.60	4.65	0%
Prob of starting TB treatment after a negative test result, HIV positive with TB	0	0	89	90	0%	168	172	0%	4.51	4.66	0%
Prop of cohort who get a culture test after a positive test result	0	1	89	90	0%	169	170	0%	4.64	4.64	0%
Prop of cohort who get a second Xpert test after a negative test result	0	0	89	90	0%	169	170	0%	4.64	4.64	0%
Probability of hard-to-diagnose TB in those with a negative TB test result, HIV positive on ART	0	1	89	89	0%	168	169	0%	4.43	6.74	3%
Prob of starting TB treatment after a positive test result, HIV positive	0	1	89	89	0%	166	169	0%	4.64	4.65	0%
Prob of TB from a negative TB test result, HIV positive on ART	0	0	89	89	0%	168	169	0%	4.53	5.73	1%
Prob of mortality from out of care, HIV positive on ART with TB	0	0	89	89	0%	168	169	0%	4.36	4.78	0%
Prob of starting the negative pathway after a negative test result, HIV positive ART with TB	0	1	89	90	0%	169	169	0%	4.63	4.64	0%
Prop of cohort who access a clinic as part of the negative pathway, HIV positive on ART	0	4	89	90	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a smear microscopy test as part of the negative pathway	0	2	89	90	0%	169	169	0%	4.64	4.64	0%
Prob of TB from a positive test result, HIV negative	0	1	89	90	0%	169	169	0%	4.60	4.65	0%
Probability of hard-to-diagnose TB in those with a negative TB test result, HIV positive	0	1	89	89	0%	168	169	0%	3.74	13.77	59%
Prop of cohort who get a INH pheno test after a negative test result	0	0	89	90	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a RIF pheno test after a negative test result	0	0	89	90	0%	169	169	0%	4.64	4.64	0%
Prob of starting TB treatment after a negative test result, HIV positive on ART no TB	0	0	89	90	0%	169	170	0%	4.64	4.64	0%
Prob of starting TB treatment after a positive test result, HIV positive on ART	0	1	89	89	0%	168	169	0%	4.64	4.64	0%
Prob of TB from a negative TB test result, HIV positive	0	0	89	89	0%	168	169	0%	4.18	9.27	15%
Prop of cohort who get an antibiotic trial after a positive test result	0	4	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a INH pheno test as part of the negative pathway	0	3	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a RIF pheno test as part of the negative pathway	0	3	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of starting TB treatment following the negative pathway, HIV positive on ART with TB	0	1	89	89	0%	169	169	0%	4.63	4.64	0%
Prob of TB from a positive test result, HIV positive on ART	0	1	89	89	0%	169	169	0%	4.60	4.64	0%
Prop of cohort who get a INH pheno test after a positive test result	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of mortality (all cause) if no TB, HIV positive on ART	0	0	89	89	0%	169	169	0%	4.64	4.68	0%

Prop of cohort who get an antibiotic trial as part of the negative pathway	0	7	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of mortality (all cause) if no TB, HIV positive	0	0	89	89	0%	169	169	0%	4.62	4.87	0%
Prob of mortality with TB, HIV positive	0	0	89	89	0%	169	169	0%	4.63	4.65	0%
Prob of starting TB treatment after a negative test result, HIV positive on ART with TB	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of mortality with TB, HIV positive on ART	0	0	89	89	0%	169	169	0%	4.64	4.65	0%
Prop of cohort who get a RIF pheno test after a positive test result	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of TB from a negative TB test result, HIV negative	0	0	89	89	0%	169	169	0%	4.60	5.09	0%
Prob of starting TB treatment following the negative pathway, HIV positive on ART no TB	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of mortality with TB, HIV negative	0	0	89	89	0%	169	169	0%	4.64	4.68	0%
Prob of starting TB treatment following the negative pathway, HIV positive with TB	0	0	89	89	0%	169	169	0%	4.65	4.65	0%
Prob of mortality (all cause) if no TB, HIV negative	0	0	89	89	0%	169	169	0%	4.64	4.65	0%
Prob of mortality (all cause) if no TB, HIV positive on ART	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of mortality (all cause) if no TB, HIV positive	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Provider cost of anti-retroviral therapy, year one	9	940	89	89	0%	169	169	0%	4.64	4.64	0%
Provider cost of anti-retroviral therapy, year two	5	524	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a clinic visit	1	52	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a hospital bed day	0	4	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a hospital bed day, per night	0	4	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a hospital visit, per visit	6	580	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a visit to a private health facility, per visit	3	292	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of a clinic visit, per visit	0	29	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of nutritional supplements, per day	0	3	89	89	0%	169	169	0%	4.64	4.64	0%
Disability weights, HIV positive on ART with no TB	0	1	89	89	0%	169	169	0%	4.63	4.80	0%
Disability weights, HIV positive on ART with TB	0	3	89	89	0%	169	169	0%	4.63	4.75	0%
Disability weights, HIV positive with no TB	0	2	89	89	0%	169	169	0%	4.42	6.90	4%
Disability weights, HIV positive with TB	0	4	89	89	0%	169	169	0%	4.62	4.88	0%
Disability weights, HIV negative with TB	0	3	89	89	0%	169	169	0%	4.64	4.71	0%
Prop of cohort on DS-TB treatment (continuation phase), monthly	0	10	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort on DS-TB treatment (intensive phase), monthly	0	40	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a follow-up Xpert test while on treatment	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a DST for Rif resistance while on treatment	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a RIF pheno test	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who get a smear microscopy test during TB treatment	0	11	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility after a negative test result, HIV negative	0	10	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility after a negative test result, HIV positive	0	2	89	89	0%	169	169	0%	4.64	4.64	0%

Prop of cohort who access a private facility after a negative test result, HIV positive on ART	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility as part of the negative pathway, HIV positive	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility as part of the negative pathway, HIV positive ART	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility after a positive test result, HIV negative	0	2	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility after a positive test result, HIV positive	0	1	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort who access a private facility after a positive test result, HIV positive on ART	0	3	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort starting MDR-TB treatment after negative test result, HIV negative	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort starting MDR-TB treatment after a negative test result, HIV positive on ART	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prop of cohort starting MDR-TB after being out-of-care, HIV negative	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Provider cost of DS-TB treatment (time dependent function), monthly	4	395	89	89	0%	169	169	0%	4.64	4.64	0%
Patient cost of accessing DS-TB treatment, time dependent function	16	1557	89	89	0%	125	1195	73%	4.64	4.64	0%
Patient cost of accessing MDR-TB treatment, time dependent function	19	1881	89	89	0%	164	229	0%	4.64	4.64	0%
Patient cost of illness, while on DS-TB treatment, time dependent function	4	409	89	89	0%	156	436	5%	4.64	4.64	0%
Patient cost of illness, while on MDR-TB treatment, time dependent function	3	329	89	89	0%	166	177	0%	4.64	4.64	0%
Prob of starting TB treatment after a negative test result, HIV negative no TB	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Prob of starting TB treatment after a negative test result, HIV negative with TB	0	0	89	89	0%	169	169	0%	4.64	4.64	0%
Discount rate	0	0	88	90	0%	165	171	0%	4.40	4.76	0%

In the Table, prop refers to the proportion of the population, while prob is the probability of an event occurring.

CHAPTER 8: DISCUSSION AND CONCLUSION

8.1 Introduction

The overarching aim of the thesis was to use an empirical example to explore ways of extending the evaluative space of economic evaluation to improve its application to local-level policy development, by exploring how the behaviour of healthcare workers may be analysed within the framework of a cost-effectiveness analysis. The example of investments supporting the TB diagnostic algorithm in South Africa was used. This allows us to identify possible policy leverage points, by exploring the proportion of additional benefit achievable through investment. The study aimed to understand these dynamics by evaluating the cost-effectiveness of health systems investments to strengthen the TB diagnostic pathway in South Africa. The work was conceptualised based on the first evaluation of Xpert MTB/RIF (a new TB diagnostic) in South Africa, which found that the test was not effective and cost neutral when implemented in routine care settings.

In this thesis, I set out to meet the following objectives, to:

1. Develop a conceptual framework, describing the TB diagnostic related interactions, between healthcare workers and the system within which they work;
2. Estimate the economic burden of TB diagnosis and treatment in South Africa;
3. Develop a mathematical model representing the TB diagnostic pathway in South Africa, with an emphasis on the decision points of healthcare workers;
4. Determine the cost-effectiveness (from a societal perspective) of complementary investments to support the implementation of new TB diagnostic tests in South Africa; and to
5. Propose and reflect on approaches for modelling how healthcare workers' behaviour in response to the resources available to them will alter the value of the implementation of new TB diagnostic technologies.

In the remainder of this chapter, the main findings of each of the objectives will be discussed individually. This will be followed by a reflection on the contributions made by the work presented in this thesis and in the last section, the limitations, policy implications and future research will be discussed.

8.2 Main findings, strengths and limitations

In this section, the main findings are discussed, with reference to the study objectives as well as the theoretical framework presented in Chapter 3. The framework from Chapter 3 is reproduced here in Figure 28, showing the relationships between the objectives of the thesis. Each of sub-sections includes a discussion outlining the strengths and limitations of the analysis pertaining to the relevant section of the work as well as a reflection of alternative analytical approaches. The chapter is concluded with a section on the contributions of the thesis and recommendations for future work, followed by the conclusions drawn from the work presented.

8.2.1 The economic burden of TB diagnosis and treatment

This section relates to Objective 2 of the thesis and was addressed in Chapter 5. The analysis presents the results of a longitudinal patient cost study and was used in the parameterisation of the mathematical model presented in Chapter 4. The policy value of empirical patient cost studies, is that they are a tool that can be used to aid decision making when comparing disease priorities for investment. Importantly, it provides an opportunity for determining the appropriate levels of support services that are needed, as well as for monitoring whether patients are able to access the services that they need (104). Tuberculosis is the archetypical poverty-related disease, with the poorest 40% of the South African population bearing 65% of the disease burden (5). TB patient cost studies therefore have an important contribution to make in designing poverty-sensitive policies for TB control. However, the relationship between TB and poverty also raises important methodological challenges that need to be taken into account to provide meaningful advice to policy makers but are often overlooked. The results of the work that forms part of this thesis, are contextualised in relation to the way in which the field has moved forward since publication, while also identifying remaining gaps for further

research. In the last part of this section, some of the methodological challenges in producing policy-relevant advice, based on patient cost studies will be discussed.

Out-of-pocket costs

The economic burden of a disease is an expression of the transport costs as well as any service fees (out-of-pocket costs) incurred by individuals when accessing care. It also includes the opportunity cost of the time spent by individuals when attending health services. Given that public primary health care is provided free of charge at the point of service in South Africa, the primary driver of out-of-pocket and time costs, is the number of healthcare visits needed to be made by a patient in seeking care for a specific disease. The number of visits is determined by the organisation of health services as well as well as by the implementation of guidelines (see Figure 7). In some settings, how services were organised, significantly contributed to the cost burden on patients, especially where there were multiple visits if HIV positive with TB (355). The theory related to the valuation of time is discussed in detail in Chapter 5. In addition to the out-of-pocket and time costs, the cost of nutritional supplements as well as the costs incurred by caregivers or the cost of someone to take over job-related tasks are added to quantify the economic burden on the household. The work presented in Chapter 5 highlights the importance of income loss in fuelling the medical poverty trap experienced by patients and their households. An important finding from the study, was the discrepancy between when patients were experiencing the greatest income loss, in the period before starting treatment, and when they were able to access cash transfers which was during the continuation phase of treatment.

In South Africa, several TB patient cost studies have been conducted, with the exception of the study reported in Chapter 5, the majority of the studies had been cross-sectional, interviewing individual patients at a single point in time (257,289,355–357). It is notable, that with the exception of one study (257), the studies largely focused on drug-sensitive TB treatment. The estimate monthly out-of-pocket costs incurred by patients ranged between \$7.06 and \$21.72, with \$56.00 per month if patients had drug-resistant Tuberculosis. Our study found that the greatest cost burden was during the diagnostic phase. The time taken to access care was reported as high across studies, with the indirect costs (or opportunity costs of time) accounting for between 55% and 86% of total

participant costs (355). Across the studies the average monthly income of patients interviewed was very low, ranging between \$76.05 and \$150.00. Up to a third of patients reported no income, with an additional 12% reporting government grants as their primary source of income. Large income losses of between 50% and 86% of reported income as a result of TB illness and care seeking. In our study, we surprisingly did not see the expected increases in productive income in the continuation phase of treatment as had been shown in other settings (355,356).

Opportunity cost of time and measures of catastrophic costs

Verguet et al. 2017. showed that investment in expanding access to TB care and improvement in treatment, could potentially reduce the number of households experiencing catastrophic costs by 5%, 18% and 18% among the poorest households (358). The notion of catastrophic costs has been conceptualised as a threshold of costs over income. But these thresholds have been found to be highly context specific, differing substantially between households (359). Goudge et al. 2009. argued that for some households, costs contributing as little as 4% of income will be catastrophic while for others, 30% will not be enough to drive the household into poverty (200). Whether households will be driven into the medical poverty trap is dependent on what the other stressors on households are and mediated by their ability to rally resources. Households may respond by for example reducing consumption, changing nutrition by buying less meat for example, or by selling assets (289). Across the studies, poor access to the South African cash transfer (the disability grant) were reported with only between 0% and 5% of respondents accessing grants. Ramma et al. found that only 16% of patients with drug-resistant TB patients accessed grants during the intensive phase of treatment as opposed to 46% during the continuation phase, with none during hospitalisation (257). Not all of the studies included the costs of caregiving, but where they did, significant amounts of caregiving were reported. A challenge related to including this cost, and one of the implications of poverty, is in how we value time spent in monetary terms. From the perspective of the State, valuing a caregiver's time based on their income prior to taking over as caregiver may underestimate the potential value of their time or fully value their potential income had they not left formal employment to care for an ill family member. However, if the person has not been employed prior to caregiving (and within the context of large-scale unemployment in the country), their time may not be valued, and no

opportunity cost may be attached to shifting care work onto available “free” labour. Furthermore, it has been shown that informal caregiving negatively impacts the wellbeing of the caregiver. Currently, while the evidence on the impact of informal caregiving on the productivity – and wellbeing loss of informal caregivers has been studied in developed countries and is sometimes included in decision-making (162,360), there is a paucity of such work in low-and-middle income country (LMIC) settings. It is possible that the burden on the wellbeing of resource constrained households would be even more pronounced and could further deepen the medical-poverty trap.

8.2.2 Cost-effectiveness of investments to support TB diagnosis

This section relates to Objectives 1, 3 and 4 of the thesis. The conceptual framework for the model is shown in Chapter 4, as well as the methodology used in the development of the model. Chapter 6 presents the results of the cost-effectiveness analyses, followed by additional analyses to identify policy levers in Chapter 7.

The investment in and the implementation of Xpert MTB/RIF into routine care settings has been widely discussed and analysed (79,221,235,310,361,362). Many countries conducted implementation studies following the roll-out of Xpert, and this has provided a rich field for studying TB diagnostic capacity and treatment initiation in countries. It is an interesting case study as raises important points about how guidelines are developed and implemented globally (135). In addition, given the number of cost-effectiveness analyses concluding that implementation in high-TB burden countries would be cost-effective, the results of the analyses based on routine care data finding that, in South Africa, it is likely to be cost neutral – highlights important cautionary points in our current use of economic evaluation at a global level for making implementation decisions. South Africa adopted Xpert as a test following international recommendations, and while the evidence does not suggest that the investment was not appropriate, it is a good case study for highlighting the importance of the configuration of the health system in assessing the value of a test and where to invest in the future. A question that may be asked following the results of the within-trial -and the model analyses presented here, is whether it is more cost-effective to invest in interventions that would strengthen the system around a new technology or to invest in a novel test? So, for example, as new TB diagnostic tests are

now entering the development pipeline, should South Africa invest in these tests or rather strengthen systems around the currently implemented tests? The results of the analysis presented in this thesis, suggests that investment to support current technology may be highly cost-effective with up to \$100 that could be spent per person per interaction with the health system without exceeding even very conservative cost-effectiveness thresholds. It is important that these investments be considered alongside new technologies during priority setting.

The work also highlights the importance of identifying policy leverage points along the pathway and then structuring interventions based on whether those leverage points would be amenable to further investment or would need large scale reforms to the system.

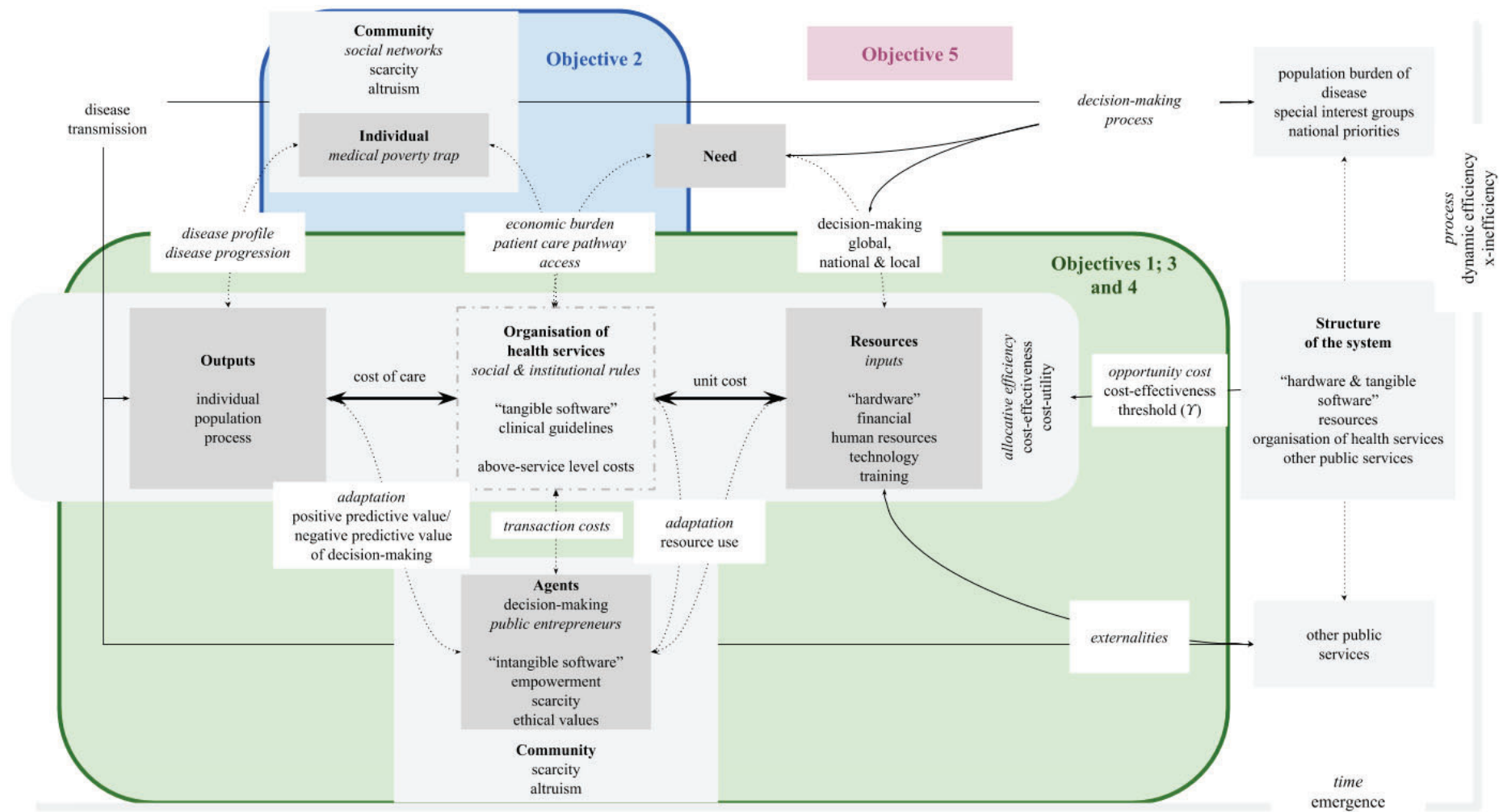


Figure 28. Theoretical framework of the thesis reproduced from Chapter 3.

8.2.3 Approaches to incorporate health systems in cost-effectiveness analysis

In this thesis, the impact of the behaviour of health care workers on the value of the TB diagnostic algorithm is investigated in three ways, by:

- using data from a pragmatic randomised control trial to describe how patients move through the patient care pathway in routine care, as well as the associated costs incurred;
- developing a conceptual framework based on available literature of the behavioural drivers of decision making related to diagnostics; and
- exploring how different elements in that decision may influence the value of the diagnostic algorithm.

On the relationship between the resources and the outcomes, there was large variation between the clinical guidelines and how these were implemented in public health facilities. Where we estimated how the transaction cost incurred during an interaction between a healthcare worker and a patient would shift the prioritisation of certain investments over others, we saw that large transaction costs were required (up to \$100 per person) to shift the curve with negative pathway investment as initiating ART having a reduced probability of being the optimal investment. In considering how the ability of healthcare workers to correctly identify those who should be prioritised for further examination after a negative test result, impact on the outcomes at a cohort level, we found that each decision in that chain was important to improve outcomes. In considering how the ability of healthcare workers to correctly identify those who should be prioritised for further examination after a negative test result, impacts on the outcomes at a cohort level, we found that each decision in that chain was important to improve outcomes. So, for example, health care workers being more likely to identify someone correctly for further test would increase the cost of the algorithm but would not lead to population level improvement unless in the next interactions with healthcare workers, the patient was also started on treatment.

Similarly to what Abimbola found in a study of TB diagnosis in Nigeria, any additional study visits required, did not only increase the cost to patients of accessing services but also prolonged productivity loss (104). Understanding what impact these interventions

would have on patient cost though is more complex than presented in the framework. In the patient cost study, it was found that patients would not only lose their own income but would also rely heavily on their social networks to assist in informal lending. The current version of the framework focuses on the interactions with the health system but could have extended to include the interactions related to other social services received (including the disability grant). Within the economic evaluation literature, however, there is an active debate related to how best to evaluate investments where the costs and effects fall outside of the health system but are crucial in the production of health (32).

Another area of important developments as this thesis was being written is the area of debate on how best to estimate the opportunity cost of competing investments (24,363,364). Some have argued that the marginal productivity of the health system should be estimated, while others have seen the threshold as a “willingness-to-pay” concept whereby a value is attached to (either historically or negotiated) an improvement of wellbeing. While these recommendations are sensible where economic evaluation is being used as part of a health technology assessment (HTA) process, evaluating more complex investments in health systems raises additional challenges. These include, how to consider the decisions of different payers or funders who are optimising against different budget constraints. During the evaluation, the challenge of conceptualising the causal relationship between investment in health systems and health outcomes. Some have therefore argued for the importance of not only considering the impact of investments on health outcomes, but also on strengthening processes in the system (365). Using the example of TB diagnosis, one would therefore not only be interested in the cost per death averted or cost per DALY averted, but would also consider the cost per patient diagnosed or the cost per patient correctly started on treatment.

8.2.4 The mathematical modelling framework

A strength of the economic work is that it was conducted alongside a pragmatic cluster randomised control trial, during the second phase of the national roll-out of the technology platform, into the existing national laboratory service. This allowed for the training of human resources and lessons from phase one to first permeate the system before the formal evaluation was conducted (366). The infrastructure of the trial was used to collect and analyse economic data. The value of conducting the study alongside a

pragmatic trial was that it captured the clinical decision-making of health care workers, as they were providing routine services. The trial also allowed us to increase the sample size of the patient cost study. However, the design of the trial constrained the interview interval and some of causal pathways between trial outcomes, and the outcomes used to estimate cost-utility were not included in the investigation. Additional model calibration and validation procedures were conducted to refine these causal pathways. A particular strength of this trial was the low trial loss-to-follow-up and thus missing data, as well as the methodical process to collect data on the clinical outcomes of each and every participant (12).

Despite the sample we were able to enrol, estimating conditional probabilities for such detailed processes for the same people over time, meant that the sample size for observations of end processes was sometimes small and categories had to be collapsed, possibly losing some detail in the analysis. Given the pragmatic nature of the trial design and the trial end-point, 6 months after first diagnostic test, it was not possible to interview the same set of patients from diagnosis through to the end of treatment. In addition, the trial was sampling patients identified with probable TB, the trial had a TB prevalence of approximately 6%, thus under sampling from those who truly had TB. A longitudinal patient cohort was constructed by interviewing one cohort at the time of sputum collection and again at their 6-months visits. The second cohort was sampled from the same health facilities at the point of transitioning from the intensive to the continuation phase (2 months) of TB treatment, with a follow up interview conducted at the end of the treatment (5 months). In constructing the cohort for the patient cost analysis, we made a simplifying assumption by assuming that the patients in the TB treatment cohort was the same as those in the presumptive TB cohort started on treatment at the same facilities. Given our sample size, we were not therefore able to comprehensively explore patient-level heterogeneity in more detail.

While the modelling framework used has many important strengths, it was possibly less flexible than might have been possible if coded in a different platform to facilitate integration of a Bayesian resampling approach to estimate the unknown parameters, and the uncertainty around them. The challenge with more complex economic models is to bring the precision needed for the economic outputs – especially in terms of predicting specific resource needs into the future, and uncertainty estimates around decisions against

a structure that allows for modelling the dynamic interactions of people moving into and out of care (367). This is likely to particularly affect the uncertainty estimates in the results presented – possibly overestimating the uncertainty in this decision.

8.3 Contributions of this thesis

This thesis contributes to the existing body of knowledge empirically and methodologically. The empirical contributions include one of the few patient cost studies to follow TB patients over time, therefore quantifying how patient income changes through different phases of TB diagnosis and treatment. The model analysis further shows that investing in health systems to support the implementation of new TB diagnostic is highly cost-effective when compared against other recent investments made in the health system.

The methodological contribution of the thesis relates to exploring an approach for expressing mechanisms interacting between macro- and micro-level interactions relating to patients' pathways through care. It does this by conceptualising the causal pathway between health systems strengthening and patient health outcomes. This conceptualisation was then used to model agent-behaviour in a state-transition model for decision making. Utility functions were constructed, to explore how behaviour may amend the value of an investment, using a combination of three approaches;

- empirically from the data on cost, resource use and health outcomes collected during a pragmatic cluster randomised control trial;
- calibration of modelled estimates to pragmatic data; and
- development of a conceptual framework based on the available literature representing interactions as well as theory.

Furthermore, this study builds on previous cost-effectiveness work of TB diagnosis, by estimating the cost-effectiveness of supportive health systems investments to support TB diagnosis in South Africa.

8.4 Recommendations for future work

Mathematical models have the potential to make valuable contributions to the study of the impact of health systems strengthening investments on the value of clinical guidelines. This work shows an approach to studying these effects and raised some interesting areas for further study.

The work presented here, highlighted the discrepancies between where patients incur the greatest economic burden if they have TB, and where further financial support is provided by the State. One of the policy outcomes of the work was a commitment by the SASSA (South African Social Security Agency) grants agency to consider ways of closing this gap, by getting the grant to those who need it earlier during treatment. However, the grant is limited in its ability to intervene in the TB poverty spiral, as it is designed and only available to those who are unable to work due to a disabling illness (very narrowly defined) – not all patients with TB will be eligible. It is still a relatively small proportion of patients with TB, who are accessing the grant (less than 10%). There is a need for further research to develop TB-sensitive cash transfers as these patients represent the most vulnerable in the population. Beyond, TB sensitive cash transfers, our work suggested that ill health could possibly also place an additional burden on the social networks of TB patients. Terreblanche (1977) first described what he called “chronic community poverty”, as a phenomenon whereby ill health, poverty and the dynamics of violence reinforces each other in communities (368). There may be potential in investigating how, and whether TB can act as an indicator and potential catalyst for community poverty, through the depletion of social networks used to support and care for those who are ill. There is a need to use such work to identify policy levers that may be used and tested in the design of broad based pro-poor policy (going beyond cash transfers), which may make a more meaningful contribution to TB control.

Health care worker behaviour in response to the implementation of interventions, could be modelled in more nuanced ways. In this model, interactions of components of the drivers of behaviour was considered, but as a next step it would be valuable to go beyond merely identifying policy levers; by modelling incentive structures and investments to amend the behaviour of healthcare workers along the diagnostic pathway.

In terms of methods of evidence synthesis, this work may also be expanded by using participatory approaches for developing the conceptual framework, for example by using processes for developing theories of change for interventions (369).

Finally, there is a gap for future work to define and empirically test the causal pathways between health systems strengthening and disease outcomes (370). In terms of model implementation, the challenge is how to model multiple interacting mechanisms that approximate interactions, emergence and adaption of investments in a way that allows for an understanding of the results. This is analogous to the challenges faced in multi-disease models.

8.5 Conclusion

TB diagnosis is a core pillar of the TB control strategy in high-burden countries, including South Africa. The study suggests that with the current diagnostic algorithm, investing in health systems strengthening approaches to support the use of TB diagnostics would be highly cost-effective. However, early diagnosis and treatment initiation may not reduce the poverty impact of TB since patients experience the greatest economic burden during the period of the start of TB-associated symptoms and in this study, patients did not regain income once started on treatment. Beyond TB sensitive cash transfers, comprehensive poverty alleviation measures may need to be considered in South Africa.

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APPENDICES

Appendix A: Patient cost study case report forms (CRFs)



Check out the Mobezi Help Centre

For tutorials, guides and examples on how to get the most out of Mobezi Researcher, spend a few minutes reviewing our [Help Centre](#). We're continually adding new material and it's the fastest, easiest way to get assistance when you need it.

CLOSE NOTICE

Screen Enrol

Last Modified by: Mobezi Support on 22 Mar 2012 17:46:59 Revision number: 433 Field Count: 282

Section 1. Variables

1.1 Screen Enrol Instruction

Complete this form whenever a new TB suspect is referred to you. You must complete this form REGARDLESS of whether the person is eligible or declines consent.

1.2 Protocol

Text

This field is not displayed on the device.

1.3 Site

Text

This field is not displayed on the device.

1.4 ParticipantID

Text

This field is not displayed on the device.

1.5 EconFlag

Numeric

This field is not displayed on the device, Value: 0

Section 2. Screening

2.1 ScreenDate

Date of Screening:

Expects a date response (required)

2.2 Gender

Gender:

Expects a single option response (required)

Male [1]

Female [2]

2.3 BirthDate

Date of birth:

Expects a date response (required)

2.4 BirthDateEstimated

Is the birth date estimated?

Expects a single option response (required)

Yes [1]

No [0]

2.5 LiveInArea

Do you live in the area?

Expects a single option response (required)

Yes [1]

No [0]

2.6 LivingInArea8Months

Will you be living in this area in the next 8 months? (Must be Yes to be eligible.)

Expects a single option response (required)

Yes [1]

No [0]

2.7 AskedToGiveSputum

Were you asked at the clinic to give a sputum (spit) specimen today?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *AskedToGiveSputum (2.7)* Equals 'No [0]'

2.8 GaveSputum

Did you provide a sputum (spit) specimen today?

Expects a single option response (required)

Yes [1]

No [0]

2.9 ExitInterviewCompleted

Have you already completed an exit interview for the XTEND study and were referred back to provide a sputum specimen? (Must be No to be eligible.)

Expects a single option response (required)

Yes [1]

No [0]

2.10 CurrentlyOnTBTreatment

Are you currently on TB treatment? (Must answer No to be eligible.)

Expects a single option response (required)

Yes [1]

No [0]

Section 3. Enrolment

3.1 Eligible

Numeric

This field is not displayed on the device.

3.2 Reset Eligibility

Operator

This field is not displayed on the device, Operator: Set(Eligible (3.1) ,1)

Prerequisites

Skip when *LiveInArea (2.5)* Equals 'Yes [1]'

3.3 LiveInArea Check

The person is not eligible for the study as they do not live in the area.

Prerequisites

Skip when *LiveInArea (2.5)* Equals 'Yes [1]'

3.4 Ineligible LiveInArea

Operator

This field is not displayed on the device, Operator: Set(Eligible (3.1) ,0)

Prerequisites

Skip when *LivingInArea8Months (2.6)* Equals 'Yes [1]'

3.5 LivingInArea8Months Check

The person is not eligible for the study as they will not be living in the area in the next 8 months.

Prerequisites

Skip when *LivingInArea8Months (2.6)* Equals 'Yes [1]'

3.6 Ineligible LivingInArea8Months

Operator

This field is not displayed on the device, Operator: Set(Eligible (3.1) ,0)

Prerequisites

Skip when *AskedToGiveSputum (2.7)* Equals 'Yes [1]'

3.7 AskedToGiveSputum Check

The person is not eligible for the study as they were not asked to give sputum (spit) specimen today.

Prerequisites

Skip when *AskedToGiveSputum (2.7)* Equals 'Yes [1]'

3.8 Ineligible AskedToGiveSputum

Operator

This field is not displayed on the device, Operator: Set(Eligible (3.1) ,0)

Prerequisites

Skip when *ExitInterviewCompleted (2.9)* Equals 'No [0]'

3.9 ExitInterviewCompleted Check

The person is not eligible for the study as they have completed an Exit interview.

Prerequisites

Skip when *ExitInterviewCompleted (2.9)* Equals 'No [0]'

3.10 Ineligible ExitInterviewCompleted

Operator

This field is not displayed on the device, Operator: `Set(Eligible (3.1) ,0)`

Prerequisites

Skip when *CurrentlyOnTBTreatment (2.10)* Equals 'No [0]'

3.11 CurrentlyOnTBTreatment Check

The person is not eligible for the study as they are currently on TB treatment.

Prerequisites

Skip when *CurrentlyOnTBTreatment (2.10)* Equals 'No [0]'

3.12 Ineligible CurrentlyOnTBTreatment

Operator

This field is not displayed on the device, Operator: `Set(Eligible (3.1) ,0)`

Prerequisites

Skip when *Eligible (3.1)* Equals '1'

3.13 Ineligible

No further information will be captured and this person will not be enrolled. If any of the information captured was incorrect, you may step back and modify it.

Expects a single option response (required)

OK [OK]

Branches

If response Equals 'OK [OK]' then skip to *End Instruction (18.1)*

3.14 TBSuspectCohortEnrolment

Give the participant a written consent form and write the participant ID on it [## PARTICIPANT ID ##]. Did the person give written consent to participate in the XTEND study?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'Yes [1]' then skip to *Locator Instruction (4.1)*

3.15 NoEnrolmentReason

What was the reason for not consenting to participate in the XTEND study?

Expects a single option response (required)

- Inadequate compensation [1]
- Not interested in participating [2]
- No time/In a hurry [3]
- Want to think about [4]
- Study info sheet not available in client's language [5]
- Other [9]

Prerequisites

Skip when *NoEnrolmentReason (3.15)* Not Equal 'Want to think about [4]'

3.16 ConsentLTF

You may suspend this enrolment at this point and resume it if the person returns. If they return, step back and indicate whether or not they consent. If they do not return, submit this form and it will be removed.

Prerequisites

Skip when *NoEnrolmentReason (3.15)* Not Equal 'Other [9]'

3.17 NoEnrolmentReasonSpecify

Please specify why the person does not consent:

Expects a single line text response (required)

3.18 NoConsent

No further information will be captured and this person will not be enrolled. If any of the information captured was incorrect, you may step back and modify it.

Expects a single option response (required)

- OK [OK]

Branches

If response Equals 'OK [OK]' then skip to *End Instruction (18.1)*

Section 4. Locator

4.1 Locator Instruction

Complete the paper-based PARTICIPANT LOCATOR form now. The participant ID is ## OVERRIDE WITH PID ##. You will need to capture this information into the mobile locator form which will be generated once you submit this participant's enrolment information.

Section 5. Demographics

5.1 CountryBirth

Participant country of birth?

Expects a single option response (required)

- South Africa [1]
- Lesotho [2]
- Swaziland [3]
- Mozambique [4]
- Botswana [5]
- Namibia [6]
- Zimbabwe [7]
- Malawi [8]
- Other [9]

Prerequisites

Skip when *CountryBirth (5.1)* Not Equal 'Other [9]'

5.2 CountryBirthOther

Specify:

Expects a single line text response (required)

5.3 EthnicGroup

What is your ethnic group?

Expects a single option response (required)

- Black/African [1]
- Coloured [2]
- Indian/Asian [3]
- White/European [4]
- Other [9]

Prerequisites

Skip when *EthnicGroup (5.3)* Not Equal 'Other [9]'

5.4 EthnicGroupOther

Specify:

Expects a single line text response (required)

5.5 HighestEducationCompleted

What is the highest level of education you have completed?

Expects a single option response (required)

- Pre-school [1]
- Grade 1-3 [2]
- Grade 4-7 [3]
- Grade 8-11 [4]
- Grade 12 [5]
- Matric with Technical Qualification or Diploma [6]
- Bachelors [7]
- Masters/Doctoral [8]
- Other [9]

Prerequisites

Skip when *HighestEducationCompleted (5.5)* Not Equal 'Other [9]'

5.6 HighestEducationCompletedOther

Specify:

Expects a single line text response (required)

5.7 MaritalStatus

What is your marital status?

Expects a single option response (required)

- Single never married [1]
- Married [2]
- Married and currently separated [3]
- Cohabiting [4]
- Divorced [5]
- Widow/er [6]

5.8 MainIncomeSource

What is your main source of income (choose only one)?

Expects a single option response (required)

- Formal employment [1]
- Self-employment [2]
- Odd jobs [3]
- Government grant (childhood/disability etc.) [4]
- Income from Investments [5]
- Maintenance [6]
- Student/scholar/learner [7]
- Pensioner [8]
- No Income [9]
- Other [99]

Prerequisites

Skip when *MainIncomeSource* (5.8) Not Equal 'Other [99]'

5.9 **MainIncomeSourceOther**

Specify:

Expects a single line text response (required)

5.10 **AverageMonthlyIncome**

On average, what is your monthly income?

Expects a single option response (required)

- Less than ZAR 600 [1]
- ZAR 601-1000 [2]
- ZAR 1001-2000 [3]
- ZAR 2001-4000 [4]
- Greater than ZAR 4000 [5]
- Don't know [6]

5.11 **OtherMemberSteadyJob**

Does anyone else in your household have a regular job?

Expects a single option response (required)

- Yes [1]
- No [0]

5.12 **DwellingType**

What type of dwelling do you live in?

Expects a single option response (required)

- House or brick/concrete block structure on separate stand or yard or on a farm [1]
- Traditional dwelling/hut/structure made of traditional materials [2]
- Flat or apartment in a block of flats [3]
- Cluster house in complex [4]
- Townhouse (semi-detached house in a complex) [5]
- Semi-detached house [6]
- House/flat/room in backyard [7]
- Informal dwelling (shack in backyard) [8]
- Informal dwelling e.g. in an informal squatter settlement or on a farm [9]
- Room/flatlet on a property or a larger dwelling servant's quarters or granny flat [10]
- Caravan/tent [11]
- Homeless [12]
- Other [99]

Prerequisites

Skip when *DwellingType* (5.12) Not Equal 'Other [99]'

5.13 **DwellingTypeOther**

Specify:

Expects a single line text response (required)

5.14 Tenure

What is the occupational status of your household?

Expects a single option response (required)

- Owned, fully paid off [1]
- Owned, not fully paid off [2]
- Rented [3]
- Occupied rent free [4]
- Other [9]

Prerequisites

Skip when *Tenure (5.14)* Not Equal 'Other [9]'

5.15 TenureOther

Specify:

Expects a single line text response (required)

5.16 MainMaterialFloors

What is the main material of your floor?

Expects a single option response (required)

- Natural floor (earth/sand/dung) [1]
- Rudimentary floor (bare wood planks) [2]
- Finished floor (parquet/polished/ceramic tiles/cement/carpet) [3]

5.17 MainMaterialWalls

What is the main material of your walls?

Expects a single option response (required)

- Plastic or cardboard [1]
- Mud [2]
- Mud and cement [3]
- Corrugated iron or zinc [4]
- Prefab or wood [5]
- Bare brick or cement blocks [6]
- Plaster or finished [7]
- Other [9]

Prerequisites

Skip when *MainMaterialWalls (5.17)* Not Equal 'Other [9]'

5.18 MainMaterialWallsOther

Specify:

Expects a single line text response (required)

5.19 MainDrinkingWaterSource

What is the main source of drinking water for members in your household?

Expects a single option response (required)

- Piped (tap) water inside dwelling [1]
- Piped (tap) water inside the yard [2]
- Piped (tap) water on community stand [3]
- No access to piped water [4]
- Borehole [5]
- Open source (river or stream) [6]
- Other [9]

Prerequisites

Skip when *MainDrinkingWaterSource (5.19)* Not Equal 'Other [9]'

5.20 MainDrinkingWaterSourceOther

Specify:

Expects a single line text response (required)

5.21 HouseholdToiletFacility

What kind of toilet facilities does your household have?

Expects a single option response (required)

- Flush toilet connected to sewage [1]
- Flush toilet connected to septic tank [2]
- Chemical toilet [3]
- Pit toilet/latrine with ventilation (VIP) [4]
- Pit toilet without ventilation [5]
- Bucket toilet [6]
- None [7]
- Other [9]

Prerequisites

Skip when *HouseholdToiletFacility (5.21)* Not Equal 'Other [9]'

5.22 HouseholdToiletFacilityOther

Specify:

Expects a single line text response (required)

5.23 DemographicsInstruction

Does your household have any of the following in working condition:

5.24 WorkingElectricGas Stove

Electric/gas stove:

Expects a single option response (required)

- Yes [1]
- No [0]

5.25 WorkingVacuumCleaner

Vacuum cleaner:

Expects a single option response (required)

Yes [1]

No [0]

5.26 WorkingWashingMachine

Washing machine:

Expects a single option response (required)

Yes [1]

No [0]

5.27 WorkingSatelliteTelevision

Satellite television:

Expects a single option response (required)

Yes [1]

No [0]

5.28 WorkingDVDPlayer

DVD player:

Expects a single option response (required)

Yes [1]

No [0]

5.29 WorkingMotorCar

Motorcar:

Expects a single option response (required)

Yes [1]

No [0]

5.30 WorkingMailPostBoxBag

Mail Post box/bag:

Expects a single option response (required)

Yes [1]

No [0]

5.31 WorkingMailDeliveryAtHome

Mail delivery at home:

Expects a single option response (required)

Yes [1]

No [0]

5.32 WorkingRadio

Radio:

Expects a single option response (required)

Yes [1]

No [0]

5.33 WorkingTV

TV:

Expects a single option response (required)

Yes [1]

No [0]

5.34 WorkingComputer

Computer:

Expects a single option response (required)

Yes [1]

No [0]

5.35 WorkingRefrigerator

Refrigerator:

Expects a single option response (required)

Yes [1]

No [0]

5.36 WorkingLandlineTelephone

Landline telephone:

Expects a single option response (required)

Yes [1]

No [0]

5.37 WorkingCellphone

Cell phone:

Expects a single option response (required)

Yes [1]

No [0]

5.38 WorkingBicycle

Bicycle:

Expects a single option response (required)

Yes [1]

No [0]

5.39 WorkingMotorCycleScooter

Motorcycle or scooter:

Expects a single option response (required)

Yes [1]

No [0]

5.40 DemographicsInstruction1

Does any member of your household own any of the following:

5.41 AnyoneOwnDonkeyHorse

Donkey or horse:

Expects a single option response (required)

Yes [1]

No [0]

5.42 AnyoneOwnLivestock

Livestock (sheep cattle or goats):

Expects a single option response (required)

Yes [1]

No [0]

Section 6. Clinic Visit

6.1 GotToClinic

How did you get to the clinic today?

Expects a single option response (required)

- Walk [1]
- Bike [2]
- Bus / Taxi [3]
- Car [4]
- Train [5]
- Other [9]

Prerequisites

Skip when *GotToClinic (6.1)* Not Equal 'Other [9]'

6.2 GotToClinicOther

Specify:

Expects a single line text response (required)

6.3 DistanceToClinicFromResidence

What is the distance in kilometres from your usual residence to this clinic?

Expects a single option response (required)

- Less than 2 km [1]
- 2 - 5 kms [2]
- 5 - 10 kms [3]
- More than 10 kms [4]

6.4 TimeToClinicFromResidence

How long did it take to get from your home to this clinic today (one way)?

Expects a time response (required)

6.5 HowMuchTransport

In total, how much did you pay for transport to the clinic today (one way)? [Fieldworker: Enter 000 if no cost.]

Expects a decimal response (required)

6.6 HowManyAdultsToday

How many adults accompanied you to the clinic today? [Fieldworker: Enter 0 if none]

Expects a numeric response (required)

6.7 CurrentCough

Do you currently have Cough?

Expects a single option response (required)

- Yes [1]
- No [0]

Prerequisites

Skip when *CurrentCough (6.7)* Equals 'No [0]'

6.8 CoughDuration

How long have you been coughing (in weeks)?

Expects a numeric response (required)

6.9 CurrentNightSweats

Do you currently have Drenching Night Sweats?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentNightSweats (6.9)* Equals 'No [0]'

6.10 NightSweatsDuration

How long have you had drenching night sweats (in weeks)?

Expects a numeric response (required)

6.11 CurrentUnintentionalWeightLoss

Do you currently have Unintentional Weight Loss?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentUnintentionalWeightLoss (6.11)* Equals 'No [0]'

6.12 UnintentionalWeightLossDuration

How long have you had unintentional weight loss (in weeks)?

Expects a numeric response (required)

6.13 CurrentFever

Do you currently have Fever?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentFever (6.13)* Equals 'No [0]'

6.14 FeverDuration

How long have you had fever (in weeks)?

Expects a numeric response (required)

6.15 CurrentHaemoptysis

Do you currently have Haemoptysis (coughing up blood)?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentHaemoptysis (6.15)* Equals 'No [0]'

6.16 HaemoptysisDuration

How long have you had Haemoptysis (in weeks)?

Expects a numeric response (required)

6.17 CurrentChestPain

Do you currently have Chest Pain?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentChestPain (6.17)* Equals 'No [0]'

6.18 ChestPainDuration

How long have you had Chest Pain (in weeks)?

Expects a numeric response (required)

6.19 CurrentShortnessofBreath

Do you currently have Shortness of Breath?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentShortnessofBreath (6.19)* Equals 'No [0]'

6.20 ShortnessofBreathDuration

How long have you had Shortness of Breath (in weeks)?

Expects a numeric response (required)

6.21 CurrentTiredness

Do you currently have Tiredness?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *CurrentTiredness (6.21)* Equals 'No [0]'

6.22 TirednessDuration

How long have you had Tiredness (in weeks)?

Expects a numeric response (required)

6.23 OtherSymptom

Do you currently have any Other symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *WhereToFirst (6.26)*

6.24 CurrentOtherSymptom1

Symptom1:

Expects a single line text response (required)

6.25 OtherSymptom1Duration

How long have you had **CurrentOtherSymptom1 (6.24)** (in weeks)?

Expects a numeric response (required)

6.26 WhereToFirst

Where was the first place you went to ask for help about your current symptoms?

Expects a single option response (required)

Pharmacy [1]

Public Clinic [2]

Private Doctor [3]

Public Hospital [4]

Traditional Healer [5]

Other [9]

Prerequisites

Skip when *WhereToFirst (6.26)* Not Equal 'Other [9]'

6.27 WhereToFirstOther

Specify:

Expects a single line text response (required)

6.28 WhereToFirstDate

When did you go to that first place (if this is your first visit indicate today's date)?

Expects a date response (required)

6.29 FirstHealthFacilityDate

When did you first attend a health facility (public sector clinic, private doctor or hospital) for your current symptoms (if this is your first visit, indicate today's date)?

Expects a date response (required)

6.30 PriorSputumGiven

Prior to today, have you provided a sputum (spit) specimen in relation to your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *PriorSputumGiven (6.30)* Equals 'No [0]'

6.31 PriorSputumGivenDate

When did you provide this prior sputum (spit) specimen?

Expects a date response (required)

6.32 PriorChestGiven

Prior to today, have you had a chest radiograph in relation to your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *PriorChestGiven (6.32)* Equals 'No [0]'

6.33 PriorChestGivenDate

When did you have this prior chest radiograph?

Expects a date response (required)

6.34 ClinicVisitInstruction

Since the time you first had symptoms, how often did you visit the following health care providers for any of these symptoms?

6.35 NumberPharmacyVisits

How many times did you go to a Private Pharmacy?

Expects a numeric response (required)

6.36 NumberPublicClinicVisits

How many times did you go to a Public Clinic?

Expects a numeric response (required)

6.37 NumberPrivateDoctorVisits

How many times did you go to a General Practitioner?

Expects a numeric response (required)

6.38 NumberPublicHospitalInVisits

How many times did you go to a Public Hospital as an Inpatient?

Expects a numeric response (required)

6.39 NumberPublicHospitalOutVisits

How many times did you go to a Public Hospital as an Outpatient?

Expects a numeric response (required)

6.40 NumberTraditionalHealerVisits

How many times did you go to a Traditional Healer?

Expects a numeric response (required)

6.41 BestReasonForVisit

What reason best describes why you visited this clinic today?

Expects a single option response (required)

- For symptoms described above [1]
- For HIV test [2]
- For routine HIV clinic visit [3]
- Other routine chronic disease follow-up, eg diabetes / hypertension [4]
- ANC [5]
- Other [9]

Prerequisites

Skip when *BestReasonForVisit (6.41)* Not Equal 'Other [9]'

6.42 BestReasonForVisitOther

Specify:

Expects a single line text response (required)

Section 7. Medical History

7.1 EverSmokedCigarettes

Have you ever smoked more than 100 cigarettes in your life?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *MedicalHistoryInstruction (7.6)*

7.2 AgeStartSmoking

At what age did you start smoking?

Expects a numeric response (required)

7.3 SmokedInLastYear

Have you smoked any cigarettes in the last year?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'Yes [1]' then skip to *CigarettesSmokedPerDay (7.5)*

7.4 AgeStopSmoking

At what age did you stop smoking?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal 'AgeStartSmoking (7.2)'

7.5 Cigarettes SmokedPerDay

When you smoked or currently, how many cigarettes do you smoke/day?

Expects a numeric response (required)

7.6 MedicalHistoryInstruction

On average, how many of each of the following do you consume per WEEK? [Fieldworker: If None, enter 00.]

7.7 ConsumptionCansBeerCider

Cans of beer/cider:

Expects a numeric response (required)

7.8 ConsumptionPintsBeerCider

Pints of beer/cider:

Expects a numeric response (required)

7.9 ConsumptionQuartsBeerCider

Quarts/750mL of beer/cider:

Expects a numeric response (required)

7.10 ConsumptionSakiyaBeerCider

Sakiya/carton of beer/cider

Expects a numeric response (required)

7.11 ConsumptionGlassesOfWine

Glasses of wine:

Expects a numeric response (required)

7.12 ConsumptionTotsWhiskyBrandySpirits

Tots of whisky/brandy/spirits:

Expects a numeric response (required)

7.13 ConsumptionNipsWhiskyBrandySpirits

Nips (200mL) of whisky/brandy/spirits:

Expects a numeric response (required)

7.14 ConsumptionHalfJacksWhiskyBrandySpirits

Half-jacks (375mL) of whisky/brandy/spirits:

Expects a numeric response (required)

7.15 EverTreatedForTB

Have you ever been treated for TB?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EverHadHIVTest (7.19)*

7.16 TBTreatmentStartDate

When did you start TB treatment? (consider only the most recent episode of TB)

Expects a date response (required)

7.17 TBTreatmentStopDate

When did you stop TB treatment? (consider only the most recent episode of TB).

Expects a date response (required)

7.18 TotalTBEpisodes

How many times have you been treated for TB?

Expects a numeric response (required)

7.19 EverHadHIVTest

Have you ever had an HIV test?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *Height (7.29)*

7.20 WillingToShare

Would you be willing to share the result?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *Height (7.29)*

7.21 RecentHIVTestResult

What was the result of your most recent HIV test?

Expects a single option response (required)

Positive [1]

Negative [2]

Don't know [3]

Branches

If response Not Equal 'Positive [1]' then skip to *Height (7.29)*

7.22 RecentHIVTestDate

Date of most recent HIV test?

Expects a date response (required)

7.23 CD4TestResultsKnown

Do you know the results of your most recent CD4 test?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EverTakenART (7.26)*

7.24 RecentCD4Date

Date of most recent CD4 test?

Expects a date response (required)

7.25 RecentCD4Result

Result of most recent CD4 test?

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Response must be *Less Than or Equal '5000'*

7.26 EverTakenART

Have you ever taken ART?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *Height (7.29)*

7.27 CurrentlyTakingART

Are you currently taking ART?

Expects a single option response (required)

Yes [1]

No [0]

7.28 ARTStartDate

When did you start ART? (most recent time if more than once)

Expects a date response (required)

7.29 Height

Height (cms)

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '100'*

Response must be *Less Than or Equal '220'*

7.30 Weight

Weight (kgs)

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '35'*

Response must be *Less Than or Equal '200'*

7.31 KarnofskyScore

Karnofsky score:

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Response must be *Less Than or Equal '100'*

Section 8. Econ Cohort

Prerequisites

Skip when *EconFlag (1.5)* Equals '0'

8.1 IsSelectedForEcon

This participant has been selected for the economics cohort. This will require an additional set of questions to be captured. Press Next to continue.

Prerequisites

Skip when *EconFlag (1.5)* Equals '1'

8.2 NotSelectedEcon

This participant has not been selected for the economics cohort. No further questions will be captured.

Expects a single option response (required)

Noted - continue [1]

Branches

If response Equals 'Noted - continue [1]' then skip to *End Instruction (18.1)*

Section 9. Private Pharmacy

9.1 PharmacyVisit

Have you had to visit a private pharmacy as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches:

If response Equals 'No [0]' then skip to *PublicClinicVisit (10.1)*

9.2 PharmacyTransport

What is the main mode of transport taken on your last visit to your usual private pharmacy?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

9.3 PharmacyCostTrans

What was the total cost of transportation (round trip) when you last visited your usual private pharmacy? [Fieldworker: Enter 000 if no cost]

Expects a decimal response (required)

Constraints:

Response must be Greater Than or Equal '0'

9.4 PharmacyTimeTravel

How much time in total did you spend travelling (round trip) when you last visited your usual private pharmacy?

Expects a time response (required)

9.5 PharmacyTimeIn

How much time did you spend in the private pharmacy on your last visit?

Expects a time response (required)

9.6 PharmacyAccompanied

How many adults accompanied you to your usual private pharmacy on your last visit?

Expects a numeric response (required)

9.7 PharmacyDrugsCost

How much have you spent on medications or other consumables in total (for all visits) at the private pharmacy since the onset of your symptoms?

Expects a decimal response (required)

Constraints:

Response must be Greater Than or Equal '0'

Section 10. Public Clinic

10.1 PublicClinicVisit

Excluding today's visit, have you had to visit a public clinic as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *PrivateClinicVisit (11.1)*

10.2 UsualClinic

Is this clinic your usual clinic?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'Yes [1]' then skip to *PublicClinicTimeIn (10.6)*

10.3 PublicClinicTransport

What is the main mode of transport taken on your last visit to your usual public clinic?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

10.4 PublicClinicCostTransport

What was the total cost of transportation (round trip) when you last visited your usual public clinic? [Fieldworker: Enter 000 if no cost.]

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

10.5 PublicClinicTimeTravel

How much time in total did you spend travelling (round trip) when you last visited your usual public clinic?

Expects a time response (required)

10.6 PublicClinicTimeIn

How much time did you spend in the public clinic on your last visit?

Expects a time response (required)

10.7 PublicClinicAccompanied

How many adults accompanied you to your usual public clinic on your last visit?

Expects a numeric response (required)

10.8 PublicClinicDiagTest

How much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the public clinic since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

Section 11. General Practitioner (GP)

11.1 PrivateClinicVisit

Have you had to visit a GP as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *OutpatientVisit (12.1)*

11.2 PrivateClinicTransport

What is the main mode of transport taken on your last visit to your usual GP?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

11.3 PrivateClinicCostTransport

What was the total cost of transportation (round trip) when you last visited your usual GP? [Fieldworker: Enter 000 if no cost]

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

11.4 PrivateClinicTimeTravel

How much time in total did you spend travelling (round trip) when you last visited your usual GP?

Expects a time response (required)

11.5 PrivateClinicTimeIn

How much time did you spend at the GP on your last visit?

Expects a time response (required)

11.6 PrivateClinicAccompanied

How many adults accompanied you to the GP on your last visit?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

11.7 PrivateClinicDrugCosts

How much have you spent on medications or other consumables in total (for all visits) at the GP since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

11.8 PrivateClinicConsultFee

How much have you spent on consultation fees in total (for all visits) at the GP since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

11.9 PrivateClinicDiagTest

How much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the GP since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

Section 12. Hospital Outpatient

12.1 OutpatientVisit

Have you had to visit a hospital outpatient clinic as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *InpatientVisit (13.1)*

12.2 OutpatientTransport

What is the main mode of transport taken on your last visit to your usual hospital outpatient clinic?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

12.3 OutpatientCostTransport

What was the total cost of transportation (round trip) when you last visited your usual hospital outpatient clinic? [Fieldworker: Enter 000 if no cost]

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

12.4 OutpatientTimeTravel

How much time in total did you spend travelling (round trip) when you last visited your usual hospital outpatient clinic?

Expects a time response (required)

12.5 OutpatientTimeIn

How much time did you spend in the hospital outpatient clinic on your last visit?

Expects a time response (required)

12.6 OutpatientAccompanied

How many adults accompanied you to your usual hospital outpatient clinic on your last visit?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

12.7 OutpatientDiagTest

How much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the hospital outpatient clinic since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Section 13. Hospital Inpatient

13.1 InpatientVisit

Have you been admitted to hospital as an inpatient as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *TradHealVisit (14.1)*

13.2 InpatientTransport

What is the main mode of transport taken on your last visit to your usual inpatient department?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

13.3 InpatientCostTransport

What was the total cost of transportation (round trip) when you last visited your usual hospital inpatient clinic? [Fieldworker: Enter 000 if no cost.]

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

13.4 InpatientTimeTravel

How much time did you spend in total travelling to and from the inpatient department on your last visit?

Expects a time response (required)

13.5 InpatientAccompanied

How many adults accompanied you to your usual hospital inpatient clinic on your last visit?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

13.6 InpatientNights

How many nights did you spend in the inpatient department in total since the onset of your symptoms?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

13.7 InpatientAllVisits

In total (add all days from all adult visits), how many visitors did you have while you were an inpatient at the hospital?

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

13.8 InpatientCostsKnown

Do you know how much you paid for your inpatient visits related to your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *TradHealVisit (14.1)*

13.9 InpatientDrugCosts

How much have you spent on medications or other consumables in total (for all visits) at the inpatient department (including its pharmacy) since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

13.10 InpatientConsultFee

How much have you spent on admission and consultation fees in total (for all visits) at the inpatient department since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

13.11 InpatientDiagTest

How much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the inpatient department since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

13.12 InpatientFoodCosts

How much have you spent on food and other costs in total (for all visits) at the inpatient department since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Section 14. Traditional Healer

14.1 TradHealVisit

Have you had to visit a traditional healer as a result of your current symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *SupplementsIntro (15.1)*

14.2 TradHealTransport

What is the main mode of transport taken on your last visit to your usual traditional healer?

Expects a single option response (required)

Walk [1]

Bike [2]

Bus / Taxi [3]

Car [4]

Train [5]

Other [9]

14.3 TradHealCostTransport

What was the total cost of transportation (round trip) when you last visited your usual traditional healer? [Fieldworker: Enter 000 if no cost.]

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

14.4 TradHealTimeTravel

How much time did you spend in total travelling to and from the traditional healer on your last visit?

Expects a time response (required)

14.5 TradHealTimeIn

How much time did you spend with the traditional healer on your last visit?

Expects a time response (required)

14.6 TradHealAccompanied

How many adults accompanied on your last visit to your usual traditional healer?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

14.7 TradHealDrugs

How much have you spent on traditional medicines or other consumables in total (for all visits) at the traditional healer since the onset of your symptoms?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Section 15. Additional Questions

15.1 SupplementsIntro

Please answer the following additional questions.

15.2 Supplements

In the last month, how much have you spent on supplements to your diet because of your symptoms, i.e.: vitamins, meat, energy drinks, soft drinks, fruit, or medicines? [Fieldworker: Enter 000 if nothing spent on dietary supplements.]

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

15.3 OnMedicalAid

Are you on medical aid?

Expects a single option response (required)

Yes [1]

No [0]

Section 16. Work / Salary Before / After Falling Ill

16.1 EmpGovt

In the month prior to your current symptoms starting, were you employed by government?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpPrivate (16.7)*

16.2 DaysGovt

How many days per month were you working for government?

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Response must be *Less Than or Equal '31'*

16.3 IncomeGovt

What was your income per month from government?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

16.4 EmpGovt2

Since your symptoms started, have you had to reduce your working hours at government because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpPrivate (16.7)*

16.5 LostDaysGovt

How many days at government have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

16.6 LostIncomeGovt

How much income have you lost at government because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

16.7 EmpPrivate

In the month prior to your current symptoms starting, were you employed by private for profit sector?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpNGO (16.13)*

16.8 DaysPrivate

How many days per month were you working for the private for profit sector?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.9 IncomePrivate

What was your income per month from the private for profit sector?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.10 EmpPrivate2

Since your symptoms started, have you had to reduce your working hours in the private for profit sector because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpNGO (16.13)*

16.11 LostDaysPrivate

How many days in the private for profit sector have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.12 LostIncomePrivate

How much income have you lost in the private for profit sector because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.13 EmpNGO

In the month prior to your current symptoms starting, were you employed by an NGO?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfEmployees (16.19)*

16.14 DaysNGO

How many days per month were you working for the NGO?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.15 IncomeNGO

What was your income per month from the NGO?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.16 EmpNGO2

Since your symptoms started, have you had to reduce your working hours at the NGO because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfEmployees (16.19)*

16.17 LostDaysNGO

How many days in the NGO have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.18 LostIncomeNGO

How much income have you lost in the NGO because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.19 EmpSelfEmployees

In the month prior to your current symptoms starting, were you a self-employed (merchant), business WITH employees?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfNoEmployees (16.25)*

16.20 DaysSelfEmployees

How many days per month were you self-employed (merchant) WITH employees?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.21 IncomeSelfEmployees

What was your income per month from being self-employed (merchant) WITH employees?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.22 EmpSelfEmployees2

Since your symptoms started, have you had to reduce your working hours as self-employed (merchant) WITH employees because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfNoEmployees (16.25)*

16.23 LostDaysSelfEmployees

How many days as self-employed (merchant) WITH employees have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.24 LostIncomeSelfEmployees

How much income have you lost as self-employed (merchant) WITH employees because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.25 EmpSelfNoEmployees

In the month prior to your current symptoms starting, were you a self-employed (merchant), business with NO employees?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfHome (16.31)*

16.26 DaysSelfNoEmployees

How many days per month were you a self-employed (merchant) with NO employees?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.27 IncomeSelfNoEmployees

What was your income per month from being self-employed (merchant) with NO employees?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.28 EmpSelfNoEmployees2

Since your symptoms started, have you had to reduce your working hours as self-employed (merchant) with NO employees because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpSelfHome (16.31)*

16.29 LostDaysSelfNoEmployees

How many days as self-employed (merchant) with NO employees have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.30 LostIncomeSelfNoEmployees

How much income have you lost as self-employed (merchant) with NO employees because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.31 EmpSelfHome

In the month prior to your current symptoms starting, were you self-employed/ from home, farmer/ fishing/ agriculture?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpLabor (16.37)*

16.32 DaysSelfHome

How many days per month were you self-employed from home?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.33 IncomeSelfHome

What was your income per month from being self-employed from home?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.34 EmpSelfHome2

Since your symptoms started, have you had to reduce your working hours as self-employed from home because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpLabor (16.37)*

16.35 LostDaysSelfHome

How many days as self-employed from home have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.36 LostIncomeSelfHome

How much income have you lost as self-employed from home because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.37 EmpLabor

In the month prior to your current symptoms starting, were you a daily labourer?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpOther (16.43)*

16.38 DaysLabor

How many days per month were you a daily labourer?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.39 IncomeLabor

What was your income per month from being a daily labourer?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.40 EmpLabor2

Since your symptoms started, have you had to reduce your working hours as a daily labourer because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpOther (16.43)*

16.41 LostDaysLabor

How many days as a daily labourer have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.42 LostIncomeLabor

How much income have you lost as a daily labourer because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.43 EmpOther

In the month prior to your current symptoms starting, were you employed in any other activity?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpRetired (16.49)*

16.44 DaysOther

How many days per month were you employed in any other activity?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '31'

16.45 IncomeOther

What was your income per month from being employed in any other activity?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.46 EmpOther2

Since your symptoms started, have you had to reduce your working hours employed in any other activity because of being sick or seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *EmpRetired (16.49)*

16.47 LostDaysOther

How many days employed in any other activity have you missed since your symptoms began?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

16.48 LostIncomeOther

How much income have you lost employed in any other activity because of being sick or seeking treatment?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

16.49 EmpRetired

Are you retired?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *EmpRetired (16.49)* Equals 'No [0]'

16.50 IncomeRetired

What is your monthly pension?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

16.51 EmpDisabled

In the month prior to your current symptoms starting, were you you disabled/sick?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *InKind (16.55)*

16.52 DisabilityGrantsReceived

Did you receive any of the following sick/disability grants (choose as many as apply)?

Expects multiple selected options (required)

Disability grant [1]

HIV grant [2]

Child grant [3]

Other [9]

None [10]

Prerequisites

Skip when *DisabilityGrantsReceived (16.52)* Excludes 'Other [9]'

16.53 DisabilityGrantsReceivedOther

Please specify what other disability grants you received?

Expects a single line text response (required)

16.54 IncomeDisabled

What is the total income from these grants?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

16.55 InKind

In addition to the above, did you receive any non-monetary payments for your work?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *InKind (16.55)* Equals 'No [0]'

16.56 ValueInKind

What do you estimate is the total value of the non-monetary payments you receive on average in a month?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Section 17. Income and Care After Falling Ill

17.1 LossInKind

In the last month, since you have been ill, have you received less non-monetary payments due to a reduction in working hours because you were ill or as a result of seeking treatment?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *LossInKind (17.1)* Equals 'No [0]'

17.2 LossValueInKind

What is the estimated monetary value of the loss of non-monetary payments you would have received in the last month?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

17.3 IncomeGain

In the last month, since you have been ill, have you received any additional income, i.e. disability grants, benefits, charity donations, due to your symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *IncomeGain (17.3)* Equals 'No [0]'

17.4 IncomeGainAmount

What is the estimated monetary value of these disability grants, benefits, charity donations, etc. you have received in the last month?

Expects a decimal response (required)

Constraints

Response must be *Greater Than or Equal '0'*

17.5 CoverUsualTasks

When you are unable to work, is anyone else in your household able to take over your household tasks?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *CoverJobTasks (17.9)*

17.6 CoverUsualTasksHours

In the last month, how many hours had to be covered by others because you were unable to do your household tasks?

Expects a numeric response (required)

Constraints

Response must be *Greater Than or Equal '0'*

Response must be *Less Than or Equal '744'*

17.7 CoverUsualTasksOccupation

What is the main occupation of the person taking over your household tasks?

Expects a single option response (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired [8]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [99]

Prerequisites

Skip when *CoverUsualTasksOccupation (17.7)* Equals 'Other [99]'

17.8 CoverUsualTasksOccupationOther

Specify:

Expects a single line text response (required)

17.9 CoverJobTasks

When you are unable to work at your job, is there anyone in your household able to take over your job-related tasks?

Expects a single option response (required)

- Yes [1]
- No [0]

Branches

If response Equals 'No [0]' then skip to *Caregiver (17.15)*

17.10 CoverJobTasksList

What are these job-related tasks?

Expects multiple selected options (required)

- Self-employed (merchant) [1]
- Business with employees [2]
- Business no employees [3]
- Self-employed/ from home [4]
- Farmer/ fishing/ agriculture [5]
- House maker [6]
- Daily Labourer [7]
- Other [9]

Prerequisites

Skip when *CoverJobTasksList (17.10)* Excludes 'Other [9]'

17.11 CoverJobTasksOther

Please specify the other job-related tasks:

Expects a single line text response (required)

17.12 CoverJobTasksHours

In the last month, how many hours did this person cover your job-related tasks?

Expects a numeric response (required)

17.13 CoverJobTasksOccupation

What is the main occupation of the person taking over your job-related tasks?

Expects a single option response (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired [8]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [99]

Prerequisites

Skip when *CigarettesSmokedPerDay (7.5)* Not Equal '12'

17.14 CoverJobTasksOccupationOther

Specify:

Expects a single line text response (required)

17.15 Caregiver

Has anyone in your household had to care for you since you have been ill?

Expects a single option response (required)

- Yes [1]
- No [0]

Branches

If response Equals 'No [0]' then skip to *BorrowMoney (17.19)*

17.16 CaregiverHours

In the last month, how many hours has this person had to take care of you?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '0'

Response must be Less Than or Equal '744'

17.17 CaregiverOccupation

What is the main occupation of the person who takes care of you?

Expects a single option response (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired [8]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [99]

Prerequisites

Skip when CaregiverOccupation (17.17) Not Equal 'Other [99]'

17.18 CaregiverOccupationOther

Specify:

Expects a single line text response (required)

17.19 BorrowMoney

Did you have to borrow any money as a result of income losses associated with your symptoms or seeking treatment for them?

Expects a single option response (required)

- Yes [1]
- No [0]

Branches

If response Equals 'No [0]' then skip to End Instruction (18.1)

17.20 BorrowMoneyAmount

How much did you have to borrow?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

17.21 RepaymentAmount

What was the total amount you paid for this loan?

Expects a decimal response (required)

Constraints

Response must be Greater Than or Equal '0'

Section 18. End

18.1 End Instruction

This is your last chance to change your responses. Please select BACK if you wish to review the questions. Alternatively, select NEXT to complete the form.



Check out the Mobezi Help Centre

For tutorials, guides and examples on how to get the most out of Mobezi Researcher, spend a few minutes reviewing our [Help Centre](#). We're continually adding new material and it's the fastest, easiest way to get assistance when you need it.

CLOSE NOTICE

TB Suspects 6M Follow Up Survey

Last Modified by: Mobezi Support on 07 Nov 2012 13:47:24 Revision number: 371 Field Count: 135

Section 1. Instructions

1.1 INSTRUCTION1

Please note that you are completing this 6-month follow up for [F Name] [L Name], [Date of Birth]. Tick NEXT to confirm.

Expects a single option response (required)

Next [1]

1.2 INSTRUCTION2

Use the timeline form to ask the participant about their visit history between the time of enrolment and starting treatment.

Section 2. Variables

2.1 protocol

Text

This field is not displayed on the device.

2.2 site

Text

This field is not displayed on the device.

2.3 participantid

Text

This field is not displayed on the device.

2.4 econflag

Numeric

This field is not displayed on the device, Value: 0

Section 3. TB Results

3.1 returnforresults

At enrolment, you gave sputum for TB testing. Did you go back to the clinic to get the result of that sputum test?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'Yes [1]' then skip to *tbtxstarted* (3.4)

3.2 reasonnotreturn

Which reason best explains what happened?

Expects a single option response (required)

I felt better [1]

I got help for my symptoms somewhere else [2]

The clinic staff were unkind [3]

I did not have time to return [4]

I moved away [5]

Other [9]

Prerequisites

Skip when *reasonnotreturn* (3.2) Not Equal 'Other [9]'

3.3 reasonnotreturnother

Please specify:

Expects a single line text response (required)

3.4 tbtxstarted

Since enrolment, did you start TB treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *INSTRUCTION3* (4.14)

3.5 tbtxstartdate

Date started TB treatment:

Expects a date response (required)

Constraints

Response must be Greater Than or Equal '01/01/2012'

Section 4. TB Tx

4.1 tbtxwhere

Where did you start your TB treatment?

Expects a single option response (required)

Clinic at which you were enroled [1]

Other place [2]

Branches

If response Equals 'Clinic at which you were enroled [1]' then skip to *tbtxnowwhere (4.4)*

4.2 tbtxstartothename

What is the name of the place (clinic/hospital etc.) where you started TB treatment?

Expects a single line text response (required)

4.3 tbtxstartclosesttown

What is the closest city or town to the place (clinic/hospital etc.) where you started TB treatment?

Expects a single line text response (required)

4.4 tbtxnowwhere

Where do you get your TB treatment now/or received your medicines when taking treatment?

Expects a single option response (required)

Clinic at which you were enroled [1]

Other place [2]

Branches

If response Equals 'Clinic at which you were enroled [1]' then skip to *tbtxregimenstarted (4.7)*

4.5 tbtxnowothername

What is the name of the place (clinic/hospital etc.) where you receive your TB treatment now?

Expects a single line text response (required)

4.6 tbtxnowclosesttown

What is the closest city or town to the place (clinic/hospital etc.) where you receive your TB treatment now?

Expects a single line text response (required)

4.7 tbtxregimenstarted

What TB treatment were you started on?

Expects a single option response (required)

Pills only [1]

Pills plus injection [2]

MDR Treatment [3]

Don't know [4]

Other [9]

Prerequisites

Skip when *tbtxregimenstarted (4.7)* Not Equal 'Other [9]'

4.8 **tbtxotherreg**

Specify other regimen:

Expects a single line text response (required)

4.9 **currentlytakingtbtx**

Are you currently taking TB treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'Yes [1]' then skip to *tbtxchanged (4.11)*

4.10 **reasonstoppedtbtx**

Why did you stop taking your TB treatment?

Expects a single option response (required)

Completed TB treatment [1]

Participant decided to stop TB treatment [2]

Provider stopped TB treatment [3]

4.11 **tbtxchanged**

While you were on TB treatment, did you change to MDR TB treatment?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *toldmdrtb (4.13)*

4.12 **datetbtxchanged**

Date TB treatment was changed to MDR TB treatment:

Expects a date response (required)

Constraints

Response must be Greater Than or Equal '01/01/2012'

4.13 **toldmdrtb**

Were you ever told you had drug-resistant TB?

Expects a single option response (required)

Yes [1]

No [0]

4.14 **INSTRUCTION3**

For those NOT on TB treatment the timeframe for the following questions is from Enrolment to Today. For those ON TB treatment the timeframe for the following questions is between Enrolment and Starting TB Treatment.

Section 5. Private Pharmacy

5.1 tbsxpharmacy

Did you visit a private pharmacy for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbsxpublicclinic (6.1)*

5.2 tbsxpharmacyfreq

How many times did you visit a private pharmacy?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

5.3 tbsxpharmacyantibio

Were you given any medicines to help with your TB symptoms at your most recent private pharmacy visit?

Expects a single option response (required)

Yes [1]

No [0]

5.4 tbsxpharmacymedicines

How much did you spend on medicines at your most recent visit to the private pharmacy (in Rands)?

Expects a decimal response (required)

Section 6. Public Clinic

6.1 tbsxpublicclinic

Did you visit a public health clinic for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbsxgp (7.1)*

6.2 tbsxpublicclinicfreq

How many times did you visit a public health clinic for your TB symptoms?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

6.3 tbsxpublicclinicsputum

Were you asked to provide a sputum (spit) specimen at any of your public health clinic visits?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbsxpublicclinicxray (6.5)*

6.4 tbsxpublicclinicputumresult

Were any of the sputum tests positive for TB?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

6.5 tbsxpublicclinicxray

Did you have a chest x-ray at any of your public health clinic visits?

Expects a single option response (required)

Yes [1]

No [0]

6.6 tbsxpublicclinicantibio

Were you given antibiotics to help with your TB symptoms at any of your public health clinic visits?

Expects a single option response (required)

Yes [1]

No [0]

6.7 tbspublicclinicothertests

Did you have an HIV test at any visit to a public health clinic?

Expects a single option response (required)

Yes [1]

No [0]

Section 7. GP

7.1 tbsxgp

Did you visit a private doctor for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbsxoutpatient (8.1)*

7.2 tbsxgpfreq

How many times did you visit a private doctor for your TB symptoms?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

7.3 tbsxgpsputum

Were you asked to provide a sputum (spit) specimen at any visit to a private doctor?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbsxgpxray (7.5)*

7.4 tbsxgpsputumresult

Were any of the sputum tests positive for TB?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

7.5 tbsxgpxray

Did you have a chest x-ray at any of your visits to a private doctor?

Expects a single option response (required)

Yes [1]

No [0]

7.6 tbsxgpantibio

Were you given antibiotics for TB symptoms at any visit to a private doctor?

Expects a single option response (required)

Yes [1]

No [0]

7.7 tbsxgpconsultspent

How much did you spend on consultation fees at your most recent visit to the private doctor (in Rands)?

Expects a decimal response (required)

7.8 tbsxgpmedsspent

How much did you spend on antibiotics for your TB symptoms at your most recent visit to the private doctor (in Rands)?

Expects a decimal response (required)

7.9 tbsxgpdiagnosticspent

How much did you spend on tests at your most recent visit to the private doctor (in Rands)?

Expects a decimal response (required)

7.10 tbsxgpothertests

Did you have an HIV test at any visit to a private doctor?

Expects a single option response (required)

Yes [1]

No [0]

Section 8. Hospital Outpatient

8.1 **tbxoutpatient**

Did you visit a hospital as an outpatient for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbxinpatient (9.1)*

8.2 **tbxoutpatientfreq**

How many times did you visit a hospital as an outpatient?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

8.3 **tbxoutpatientsputum**

Were you asked to provide a sputum (spit) specimen at any visit to hospital as an outpatient?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *tbxoutpatientxray (8.5)*

8.4 **tbxoutpatientsputumresult**

Were any of the sputum tests positive for TB?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

8.5 **tbxoutpatientxray**

Did you have a chest x-ray at any of your visits to hospital as an outpatient?

Expects a single option response (required)

Yes [1]

No [0]

8.6 **tbxoutpatientantibio**

Were you given antibiotics for TB symptoms at any visit to a hospital as an outpatient?

Expects a single option response (required)

Yes [1]

No [0]

8.7 tbxoutpatientmedsspent

How much did you spend in total for your most recent visit to the hospital as an outpatient (in Rands)?

Expects a decimal response (required)

8.8 tbxoutpatientothertests

Did you have an HIV test at any visit to a hospital as an outpatient?

Expects a single option response (required)

Yes [1]

No [0]

Section 9. Hospital Inpatient

9.1 `tbxinpatient`

Have you been admitted to hospital as an inpatient for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to `tbxtrathealer (10.1)`

9.2 `tbxinpatientfreq`

How many times have you been admitted to hospital for TB symptoms?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

9.3 `tbxinpatientnightstotal`

How many nights in total have you spent in hospital?

Expects a numeric response (required)

9.4 `tbxinpatientsputum`

Were you asked to provide a sputum (spit) specimen at any stay in hospital?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to `tbxinpatientxray (9.6)`

9.5 `tbxinpatientsputumresult`

Were any of the sputum tests positive for TB?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

9.6 `tbxinpatientxray`

Did you have a chest x-ray at any stay in hospital?

Expects a single option response (required)

Yes [1]

No [0]

9.7 **tbxinpatientantibio**

Were you given antibiotics for TB symptoms at any stay in hospital?

Expects a single option response (required)

Yes [1]

No [0]

9.8 **tbxinpatientadmitspent**

How much did you spend on admission and consultation fees in total for all inpatient visits (in Rands)?

Expects a decimal response (required)

9.9 **tbxinpatientmedsspent**

How much did you spend on medicines for your TB symptoms in total as an inpatient (in Rands)?

Expects a decimal response (required)

9.10 **tbxinpatientdiagnosticspent**

How much did you spend on tests in total as an inpatient (in Rands)?

Expects a decimal response (required)

9.11 **tbxinpatientothertests**

Did you have an HIV test at any visit to a hospital as an inpatient?

Expects a single option response (required)

Yes [1]

No [0]

Section 10. Traditional Healer

10.1 tbsxtradhealer

Did you visit a Traditional Healer for any of your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *hivwillingtoshare (11.1)*

10.2 tbsxtradhealerfreq

How many times did you visit a traditional healer for TB symptoms?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

10.3 tbsxtradhealertotalspent

How much did you spend in total for all visits to the traditional healer (include value of payments in kind) (in Rands)?

Expects a decimal response (required)

Section 11. HIV Testing

11.1 hivwillingtoshare

Would you be willing to share your HIV status with us?

Expects a single option response (required)

Yes [1]

No [0]

Branches:

If response Equals 'No [0]' then skip to *currentempty6mos (12.1)*

11.2 hivnegativetestever

Have you ever tested negative for HIV?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

Branches:

If response Not Equal 'Yes [1]' then skip to *6moshivstatus (11.4)*

11.3 datenegativehivtest

Date of most recent negative HIV test:

Expects a date response (required)

11.4 6moshivstatus

Have you tested positive for HIV?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

Branches:

If response Not Equal 'Yes [1]' then skip to *currentempty6mos (12.1)*

11.5 6moshivtestdate

Date of first positive HIV test:

Expects a date response (required)

11.6 6moshivtestwhere

Where did you receive these first positive HIV test results?

Expects a single option response (required)

Clinic at which you were enrolled [1]

Other [2]

Branches:

If response Equals 'Clinic at which you were enrolled [1]' then skip to *6moscd4 (11.9)*

11.7 6moshivestvenue

What is the name of the testing venue where you received these first positive HIV test results?

Expects a single line text response (required)

11.8 6moshivesttown

What is the closest city or town to where you received these first positive HIV test results?

Expects a single line text response (required)

11.9 6moscd4

Do you know the result of your very first CD4 count?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *cd4attbtxstartdate* (11.12)

11.10 6moscd4date

Date of this CD4 test:

Expects a date response (required)

11.11 6moscd4result

Result of this CD4 test (in cells/mL₃):

Expects a numeric response (required)

11.12 cd4attbtxstartdate

Do you remember your CD4 count at the time of starting TB treatment? (Between enrolment today.)

Expects a single option response (required)

Yes [1]

No [0]

Not Applicable (not started on TB treatment) [3]

Branches

If response Not Equal 'Yes [1]' then skip to *cd4mostrecent* (11.15)

11.13 cd4attbtxtestdate

Date of this CD4 test:

Expects a date response (required)

11.14 cd4attbtxresult

Result of this CD4 test (in cells/mL₃):

Expects a numeric response (required)

11.15 cd4mostrecent

Do you know your most recent CD4 count?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *6mosstartedart (11.18)*

11.16 cd4mostrecentdate

Date of most recent CD4 test:

Expects a date response (required)

11.17 cd4mostrecentresult

Result of most recent CD4 test (in cells/mL3):

Expects a numeric response (required)

11.18 6mosstartedart

Since enrolment, have you started ART?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.19 6mosartstartdate

When did you start ART?

Expects a date response (required)

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.20 6moscurrentart

Are you currently taking ART?

Expects a single option response (required)

Yes [1]

No [0]

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.21 **artwhere**

Where did you, or do you receive your ART care?

Expects a single option response (required)

Clinic at which you were enrolled [1]

Other Public Clinic [2]

Private Doctor/GP [3]

Public Hospital [4]

NGO [5]

Branches

If response Equals 'Clinic at which you were enrolled [1]' then skip to *6moscotrimox (11.24)*

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.22 **artwhereothername**

What is the name of the facility where you receive your ART care?

Expects a single line text response (required)

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.23 **artwhereothertown**

What is the closest city or town to this facility where you receive your ART care?

Expects a single line text response (required)

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

11.24 **6moscotrimox**

Since enrolment, were you started on cotrimoxazole (Bactrim)?

Expects a single option response (required)

Yes [1]

No [0]

Unknown [3]

Prerequisites

Skip when *6mosstartedart (11.18)* Equals 'No [0]'

Skip when *6moscotrimox (11.24)* Not Equal 'Yes [1]'

11.25 **startcotrimox**

When did you start taking cotrimoxazole/Bactrim?

Expects a date response (required)

Section 12. Econ Subform

12.1 *currentemploy6mos*

Where are you currently employed? [Interviewer: Tick all that apply]

Expects multiple selected options (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired/pensioner [8]
- Receive grants (child care/foster care)/all-pay [13]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [99]

12.2 *onmedaid6mos*

Do you have medical aid?

Expects a single option response (required)

- Yes [1]
- No [0]

Branches

If response Equals 'No [0]' then skip to *currentincome6mos (12.4)*

12.3 *medcover6mos*

What medical cover do you have? (Choose one)

Expects a single option response (required)

- Hospital cover [1]
- Hospital cover AND day-to-day expenses (e.g. GP visits, medicine) [2]

12.4 *currentincome6mos*

What is your current total monthly income from all jobs (in Rands)?

Expects a decimal response (required)

12.5 workchanged6mos

Since enrolment, has your work situation changed as a result of your TB symptoms or seeking treatment for your TB symptoms? [Interviewer: Not including the period after TB treatment if Participant started TB treatment.]

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *ncomechanged6mos (12.7)*

12.6 howworkchanged6mos

How did your work situation change?

Expects a single option response (required)

No change in work [1]

Lost work/job(s) or had to quit work/job(s) [2]

Changed work (had to find a new job) [3]

Took new work (in addition to current work/job(s)) [4]

12.7 ncomechanged6mos

Since enrolment, has your monthly income changed?

Expects a single option response (required)

No change in income/stayed the same [1]

Monthly income increased [2]

Monthly income decreased [3]

Branches

If response Equals 'No change in income/stayed the same [1]' then skip to *daysworkedchanged6mos (12.10)*

Prerequisites

Skip when *ncomechanged6mos (12.7)* Not Equal 'Monthly income increased [2]'

12.8 incomeincrease6mos

By how much was your monthly income increased/month?

Expects a decimal response (required)

Prerequisites

Skip when *ncomechanged6mos (12.7)* Not Equal 'Monthly income decreased [3]'

12.9 incomedecrease6mos

By how much was your monthly income decreased/month?

Expects a decimal response (required)

12.10 daysworkedchanged6mos

Since enrolment, has the number of days worked/month changed?

Expects a single option response (required)

No change in days worked/month, stayed the same [1]

Days/month increased [2]

Days/month decreased [3]

Branches

If response Equals 'No change in days worked/month, stayed the same [1]' then skip to *timeoff6mos (12.13)*

Prerequisites

Skip when *daysworkedchanged6mos (12.10)* Not Equal 'Days/month increased [2]'

12.11 *daysworkedincrease6mos*

How many more days/month were you able to work?

Expects a numeric response (required)

Prerequisites

Skip when *daysworkedchanged6mos (12.10)* Not Equal 'Days/month decreased [3]'

12.12 *daysworkeddecrease6mos*

How many less days/month were you able to work?

Expects a numeric response (required)

12.13 *timeoff6mos*

Since enrolment, have you had to take time off from any work because of your TB symptoms or as a result of seeking treatment for your TB symptoms? (This includes time off from household or other unpaid tasks.)

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *inkind6mos (12.15)*

12.14 *daysmissed6mos*

Since enrolment, how many days of work have you missed because of your TB symptoms or seeking treatment?

Expects a numeric response (required)

Constraints

Response must be Greater Than or Equal '1'

12.15 *inkind6mos*

Since enrolment, have you gained or lost any non-monetary payments such as food, clothing, or gifts because of your TB symptoms or as a result of seeking treatment for your TB symptoms?

Expects a single option response (required)

No non-monetary payments gained or lost [1]

Non-monetary payments gained [2]

Non-monetary payments lost [3]

Branches

If response Equals 'No non-monetary payments gained or lost [1]' then skip to *jobtask6mos (12.18)*

Prerequisites

Skip when *inkind6mos (12.15)* Not Equal 'Non-monetary payments gained [2]'

12.16 *inkindgain6mos*

What is the cost of non-monetary payments you gained (in Rands)?

Expects a numeric response (required)

12.17 *inkindloss6mos*

What is the cost of the non-monetary payments you lost (in Rands)?

Expects a numeric response (required)

12.18 *jobtask6mos*

When you are unable to work at your job, did anyone in your household take over your job-related tasks?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *householdtask6mos (12.21)*

12.19 *jobtaskhours6mos*

In the last month, how many hours had to be covered?

Expects a decimal response (required)

12.20 *occupyjobtask6mos*

What is the main occupation of the person taking over your tasks? [Interviewer: Tick all that apply]

Expects multiple selected options (required)

Employed by government [1]

Employed by private for profit sector [2]

Employed by NGO [3]

Self-employed (merchant), business with employees [4]

Self-employed (merchant), business no employees [5]

Self-employed/ from home, farmer/ fishing/ agriculture [6]

Unemployed/looking for work [7]

Retired [8]

Pupil/student [9]

Disabled/sick [10]

House maker [11]

Daily labourer [12]

Other [99]

12.21 *householdtask6mos*

When you are unable to work, did anyone in your household take over your household tasks?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *caregiver6mos (12.24)*

12.22 *householdtaskhours6mos*

In the last month, how many hours had to be covered?

Expects a decimal response (required)

12.23 occupyhouseholdtaskhours6mos

What is the main occupation of the person taking over your tasks? [Interviewer: Tick all that apply]

Expects multiple selected options (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired [8]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [13]

12.24 caregiver6mos

Has anyone in your household had to care for you since you have been ill?

Expects a single option response (required)

- Yes [1]
- No [0]

Branches

If response Equals 'No [0]' then skip to *borrowmoney6mos (12.27)*

12.25 caregiverhours6mos

In the last month, how many hours had to be covered?

Expects a decimal response (required)

12.26 caregiveroccupation6mos

What is the main occupation of the person taking over your tasks? [Interviewer: Tick all that apply]

Expects multiple selected options (required)

- Employed by government [1]
- Employed by private for profit sector [2]
- Employed by NGO [3]
- Self-employed (merchant), business with employees [4]
- Self-employed (merchant), business no employees [5]
- Self-employed/ from home, farmer/ fishing/ agriculture [6]
- Unemployed/looking for work [7]
- Retired [8]
- Pupil/student [9]
- Disabled/sick [10]
- House maker [11]
- Daily labourer [12]
- Other [99]

12.27 borrowmoney6mos

Since enrolment, did you have to borrow any money as a result of income losses because of your TB symptoms or as a result of seeking treatment for your TB symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *6moscough (13.1)*

12.28 borrowmoneyamout6mos

How much did you have to borrow in total (in Rands)?

Expects a decimal response (required)

12.29 payback6mos

How much do you have to pay back in total (in Rands)?

Expects a decimal response (required)

Section 13. Current S/Sx

13.1 6moscough

Do you currently have Cough?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *6mosnightsweats (13.3)*

13.2 6moscoughduration

How long have you been coughing (in weeks)?

Expects a decimal response (required)

13.3 6mosnightsweats

Do you currently have Drenching night sweats?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *6mosweightloss (13.5)*

13.4 6mosnightsweatsduration

How long have you had drenching night sweats (in weeks)?

Expects a decimal response (required)

13.5 6mosweightloss

Do you currently have Unintentional weight loss?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to *6mosfever (13.7)*

13.6 6mosweightlossduration

How long have you had unintentional weight loss (in weeks)?

Expects a decimal response (required)

13.7 6mosfever

Do you currently have Fever?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to 6mosothersx (13.9)

13.8 6mosfeverduration

How long have you had fever (in weeks)?

Expects a numeric response (required)

13.9 6mosothersx

Do you have any other symptoms?

Expects a single option response (required)

Yes [1]

No [0]

Branches

If response Equals 'No [0]' then skip to referredback (13.12)

13.10 6mossymptom

What is the other symptom?

Expects a single line text response (required)

13.11 6mossymptomduration

How long have you had 6mossymptom (13.10) for (in weeks)?

Expects a decimal response (required)

13.12 referredback

Did you send this participant back to the clinic for investigation of current symptoms.

Expects a single option response (required)

Yes [1]

No/Not applicable [0]

Section 14. End

14.1 End

Thank you for conducting the survey. Please select BACK if you wish to review the questions. Alternatively, select NEXT to complete the survey.

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PROTOCOL NUMBER: AUR2-8-103

TITLE: XTEND STUDY

XPRT MTB/RIF FOR DIAGNOSIS OF TUBERCULOSIS: EVALUATING
IMPACT AND COST-EFFECTIVENESS IN THE ROUTINE ROLL-OUT IN SOUTH
AFRICA

DATA COLLECTION INSTRUCTIONS: SUPPLEMENT 3

SS002: TB PATIENTS 2-MOS INTERVIEW

1. Complete this paper CRF for all TB Patients eligible for enrolment who have consented. TB patients **cannot** already have participated in the Xtend TB Suspects cohort; but Exit Interviewees are eligible.
2. The TB Patient interview is completed with the TB Patient.
3. Ask each question in the order it appears on the form and choose the *best possible response* from the options provided.
4. Do not skip questions unless told to do so by the skip logic.
5. Do not mark outside of the designated response areas. Do not write notes or make marks in the margins.
6. If you make a mistake, refer to the Data Collection instructions for 'Correcting CRFs'.
7. After the interview is complete review the form to ensure all questions were answered **before ending the interview with the participant**.

Completed By:

SS002 v1 20AUG2012

Date Completed: //

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9. What is your main source of income (choose only one)?

- 1 = Formal employment
- 2 = Self-employment
- 3 = Odd jobs
- 4 = Government grant (childhood/disability, etc.)
- 5 = Income from investments
- 6 = Student/scholar/learner
- 7 = Pensioner
- 8 = No income
- 9 = Other, specify: _____

10. On average, what is your monthly income?

- 1 = < ZAR 600
- 2 = ZAR 601-1000
- 3 = ZAR 1001-2000
- 4 = ZAR 2001-4000
- 5 = > ZAR 4000
- 7 = Don't know

11. Other than yourself, does anyone in your household have a regular job?.....1=Yes, 0=No or Lives Alone

12. What type of dwelling do you live in?

- 10 = House or brick/concrete block structure on separate stand or yard or on a farm
- 11 = Traditional dwelling/hut/structure made of traditional materials
- 12 = Flat or apartment in a block of flats
- 13 = Cluster house in complex
- 14 = Townhouse (semi-detached house in a complex)
- 15 = Semi-detached house
- 16 = House/flat/room in backyard
- 17 = Informal dwelling (shack in backyard)
- 18 = Informal dwelling e.g. in an informal squatter settlement or on a farm
- 19 = Room/flatlet on a property or a larger dwelling, servant's quarters, or granny flat
- 20 = Caravan/tent
- 21 = Homeless
- 99 = Other, specify: _____

13. What is the main material of your floor?

- 1 = Natural floor (earth/sand/dung)
- 2 = Rudimentary floor (bare wood planks)
- 3 = Finished floor (parquet/polished/ceramic tiles/cement/carpet)

14. What is the main material of your walls?

- 1 = Plastic or cardboard
- 2 = Mud
- 3 = Mud and cement
- 4 = Corrugated iron or zinc
- 5 = Prefab or wood
- 6 = Bare brick or cement blocks
- 7 = Plaster or finished
- 9 = Other, specify: _____

Completed By: □□

Date Completed: □□/□□/□□□□

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15. What is the main source of drinking water for members in your household?

- 1 = Piped (tap) water inside dwelling
- 2 = Piped (tap) water inside the yard
- 3 = Piped (tap) water on community stand
- 4 = No access to piped water
- 5 = Borehole
- 6 = Open source (river or stream)

9 = Other, specify: _____

16. What kind of toilet facilities does your household have?

- 1 = Flush toilet connected to sewage
- 2 = Flush toilet connected to septic tank
- 3 = Chemical toilet
- 4 = Pit toilet/latrine with ventilation (VIP)
- 5 = Pit toilet without ventilation
- 6 = Bucket toilet
- 7 = None

9 = Other, specify: _____

17. Does your household have any of the following in working condition?

17a. Electric/gas stove: 1=Yes, 0=No

17b. Vacuum cleaner: 1=Yes, 0=No

17c. Washing machine: 1=Yes, 0=No

17d. Satellite television: 1=Yes, 0=No

17e. DVD player: 1=Yes, 0=No

17f. Motorcar: 1=Yes, 0=No

17g. Mail Post box/bag: 1=Yes, 0=No

17h. Mail delivery at home: 1=Yes, 0=No

17i. Radio: 1=Yes, 0=No

17j. TV: 1=Yes, 0=No

17k. Computer: 1=Yes, 0=No

17l. Refrigerator: 1=Yes, 0=No

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17m. Landline telephone: 1=Yes, 0=No

17n. Cell phone: 1=Yes, 0=No

17o. Bicycle: 1=Yes, 0=No

17p. Motorcycle or scooter:..... 1=Yes, 0=No

18. Does any member of your household own:

18a. Donkey or horse: 1=Yes, 0=No

18b. Livestock (sheep, cattle or goats):..... 1=Yes, 0=No

CLINIC VISIT

19. Is this the usual clinic you go to for your TB care and treatment? 1=Yes, 0=No

20. How did you get to the clinic today?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

21. What is the distance in kilometres from your usual residence to this clinic?.....

- 1 = < 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

22. How long did it take to get from your home to this clinic today (round trip)?..... (HH:MM) :

23. In total, how much did you pay for transport to the clinic today (round trip)? R
(If you did not pay for transport enter 000.)

24. How many adults accompanied you to the clinic today? **(Enter 0 if none.)**
If 0, go to question 25.

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For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

Table with 5 columns: 24a. Adult 1 main occupation, 24b. Adult 2 main occupation, 24c. Adult 3 main occupation, 24d. Adult 4 main occupation, 24e. Adult 5 main occupation. Each column has a box for a two-digit code and a row for 'If other, specify:'.

- 01 = Employed by government
02 = Employed by private for profit sector
03 = Employed by NGO
04 = Self-employed (merchant), business with employees
05 = Self-employed (merchant), business no employees
06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
08 = Retired
09 = Pupil/student
10 = Disabled/sick
11 = House maker
12 = Daily labourer
99 = Other, specify

25. In the last 2 months, how many times have you visited this clinic for any illness? (Not including today.) □□

26. In the last 2 months, how many times have you visited this clinic to collect your TB treatment? (Not including today.) □□

27. Date of first sputum provided for TB test, during this illness (not a prior diagnosis): dd/mm/yyyy □□/□□/□□□□

28. Date that you were diagnosed with TB (this episode): dd/mm/yyyy □□/□□/□□□□

29. Date of starting TB treatment (this episode): dd/mm/yyyy □□/□□/□□□□

30. What is the total duration of your planned treatment? 1 = Six months, 2 = Eight months, 3 = Eighteen months, 7 = Unknown, 9 = Other, specify: _____

31. What was your weight when you started TB treatment? (in kgs) □□□.□ If unknown, draw a line through the response field, indicate UK, initial and date.

AUR2-8-103- [] [] [] - [] [] [] [] [] []

[] [] / [] [] / [] [] [] []

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32. What was your **initial** treatment regimen: []

- 1 = Pills only
- 2 = Pills plus injection
- 3 = MDR TB Treatment
- 4 = Don't know
- 9 = Other, specify: _____

32a. How many times since you started TB treatment has your regimen been changed? [] []

32b. Did you complete your previous TB treatment? 1=Yes, 0=No []

If Yes, go to question 33.

32c. What was your reason for not completing TB treatment? []

- 1 = Participant did not have money for treatment
- 2 = Participant did not like the side effects of the treatment
- 3 = Participant moved
- 4 = The distance to the clinic/hospital was too far
- 5 = Clinic ran out of medications
- 9 = Other, specify: _____

32d. Date of most recent change of treatment regimen: dd/mm/yyyy [] [] / [] [] / [] [] [] []

32e. What is your **current** treatment regimen: []

- 1 = Pills only
- 2 = Pills plus injection
- 3 = MDR TB Treatment
- 4 = Don't know
- 9 = Other, specify: _____

33. When you were diagnosed with TB, were you referred for an HIV test? 1=Yes, 0=No []

If No, go to question 34.

33a. Did you take an HIV test as a result of this referral? 1=Yes, 0=No []

34. Would you be willing to share the result of your most recent HIV test/the test you took as a result of the referral?

..... 1=Yes, 0=No []

If No, go to question 36.

34a. What was the result of this HIV test? []

If Negative or Don't know, go to question 36.

- 1 = Positive
- 2 = Negative
- 3 = Don't know

34b. Was this your first positive test? 1=Yes, 0=No []

Completed By: [] []

Date Completed: [] [] / [] [] / [] [] [] []



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[] [] / [] [] / [] [] [] []

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35. Have you started ART?1=Yes, 0=No []

If No, go to question 35.

35a. When did you start ART?dd/mm/yyyy [] [] / [] [] / [] [] [] []

35b. Did you start ART as a consequence of your initial referral from TB services to HIV testing? ..1=Yes, 0=No []

35c. Are your visits for ART combined with your visits for TB treatment?1=Yes, 0=No []

35d. In the last 2 months, how many times have you visited this clinic to collect your ART treatment? [] []

(Not including today.)

35e. In the last 2 months, how many times have you visited another public clinic to collect your ART treatment?..

..... [] []

35f. In the last 2 months, how many times have you visited a private pharmacy to collect your ART treatment?

..... [] []

35g. In the last 2 months, how many times have you visited a general practitioner to collect your ART treatment?

..... [] []

35h. In the last 2 months, how many times have you visited a hospital outpatient clinic to collect your ART

treatment? [] []

35i. In the last 2 months, how many times have you been admitted to hospital as an inpatient because of your

ART treatment?..... [] []

36. Do you have a medical aid?1=Yes, 0=No []

If No, go to question 36.

36a. What medical cover do you have? []

1 = Hospital cover

2 = Hospital cover AND day-to-day expenses (e.g. GP visits, medicine)

OTHER PUBLIC HEALTH CLINIC

37. Have you had to visit a different public clinic as a result of your TB treatment/current symptoms? 1=Yes, 0=No []

If No, go to question 37.

37a. In the last 2 months, how many times have you visited this other public clinic as a result of your TB

treatment/current symptoms? [] []

Completed By: [] []

Date Completed: [] [] / [] [] / [] [] [] []



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37b. What is the main mode of transport taken on your last visit to this **other** public clinic?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

37c. What is the distance from your usual residence to the **other** public clinic?

- 1 = ≤ 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

37d. What was the total cost of transportation (round trip) when you last visited this **other** public clinic?

(Enter 000 if no cost.) R

37e. How much time in total did you spend travelling (round trip) when you last visited the **other** public clinic?

..... (HH:MM) :

37f. How much time did you spend in the **other** public clinic on your last visit for TB treatment/current

symptoms?..... (HH:MM) :

37g. How many adults accompanied you to the **other** public clinic on your last visit for TB treatment/current

symptoms?

If 0, go to question 38.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

37gi. Adult 1 main occupation:	37gii. Adult 2 main occupation:	37giii. Adult 3 main occupation:	37giv. Adult 4 main occupation:	37gv. Adult 5 main occupation:
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

Completed By:

Date Completed: //

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PHARMACY

38. In the last 2 months, how many times have you had to visit a private pharmacy as a result of your TB treatment/
current symptoms? □□

If 00, go to question 39.

38a. What is the main mode of transport taken on your last visit to your usual private pharmacy? □

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

38b. What is the distance from your usual residence to your usual private pharmacy? □

- 1 = ≤ 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

38c. What was the total cost of transportation (round trip) when you last visited your usual private pharmacy?
(Enter 000 if no cost.)..... R □□□

38d. How much time in total did you spend travelling (round trip) when you last visited your usual private
pharmacy?..... (HH:MM) □□:□□

38e. How much time did you spend in the private pharmacy on your last visit for TB treatment/ current
symptoms?..... (HH:MM) □□:□□

38f. How many adults accompanied you to your usual private pharmacy on your last visit for TB treatment/
current symptoms? □
If 0, go to question 38g.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

38fi. Adult 1 main occupation:	38fii. Adult 2 main occupation:	38fiii. Adult 3 main occupation:	38fiv. Adult 4 main occupation:	38fv. Adult 5 main occupation:
□□	□□	□□	□□	□□
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

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- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

38g. In the last 2 months, how much have you spent on medicine or other consumables related to your TB

treatment/current symptoms in total (for all visits) at the private pharmacy? R

38h. Did you pay for these medicines using your medical aid? 1=Yes, 0=No

GENERAL PRACTITIONER

39. In the last 2 months, how many times have you visited a **general practitioner (GP)** as a result of your TB

treatment/current symptoms?

If 00, go to question 40.

39a. What is the main mode of transport taken on your last visit to your usual **GP**?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

39b. What is the distance from your usual residence to your usual **GP**?

- 1 = ≤ 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

39c. What was the total cost of transportation (round trip) when you last visited your usual **GP**? R
(Enter 000 if no cost.)

39d. How much time in total did you spend travelling (round trip) when you last visited your usual **GP**?

..... (HH:MM) :

39e. How much time did you spend at your usual **GP** on your last visit? (HH:MM) :

39f. How many adults accompanied you to your usual **GP** on your last visit?

If 0, go to question 39g.

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Date Completed: //

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□□/□□/□□□□

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For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

Table with 5 columns for adult main occupations (39fi to 39fv) and rows for occupation codes and 'If other, specify'.

- 01 = Employed by government
02 = Employed by private for profit sector
03 = Employed by NGO
04 = Self-employed (merchant), business with employees
05 = Self-employed (merchant), business no employees
06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
08 = Retired
09 = Pupil/student
10 = Disabled/sick
11 = House maker
12 = Daily labourer
99 = Other, specify

39g. In the last 2 months, how much have you spent on medications or other consumables in total (for all visits)

at your usual GP? R □□□□

39h. In the last 2 months, how much have you spent on consultation fees in total (for all visits) at your usual

GP? R □□□□

38i. In the last 2 months, how much have you spent on diagnostic costs (including X-rays) in total (for all visits)

at the GP? R □□□□

39j. Did you pay using your medical aid? 1=Yes, 0=No □

HOSPITAL OUTPATIENT CLINIC

40. In the last 2 months, how many times have you had to visit a hospital outpatient clinic as a result of your TB

treatment/current symptoms? □□

If 00, go to question 41.

40a. What is the main mode of transport taken on your last visit to your usual hospital outpatient clinic for TB

treatment/current symptoms? □

- 1 = Walk
2 = Bike
3 = Bus/taxi
4 = Car
5 = Train
9 = Other, specify: _____

Completed By: □□

Date Completed: □□/□□/□□□□

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40b. What is the distance from your usual residence to your usual **hospital outpatient clinic**?

- 1 = ≤ 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

40c. What was the total cost of transportation (round trip) when you last visited your usual **hospital outpatient clinic**? (Enter 000 if no cost.) R

40d. How much time in total did you spend travelling (round trip) when you last visited your usual **hospital outpatient clinic**? HH:MM) :

40e. How much time did you spend in the **hospital outpatient clinic** on your last visit?... (HH:MM) :

40f. How many adults accompanied you to your usual **hospital outpatient clinic** on your last visit for TB treatment/current symptoms?
If 0, go to question 40g.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

40fi. Adult 1 main occupation:	40fii. Adult 2 main occupation:	40fiii. Adult 3 main occupation:	40fiv. Adult 4 main occupation:	40fv. Adult 5 main occupation:
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

40g. In the last 2 months, how much have you spent on medications or other consumables in total (for all visits) at the **hospital outpatient clinic** since the onset of your symptoms? R

40h. In the last 2 months, how much have you spent on consultation fees in total (for all visits) at the **hospital outpatient clinic** since the onset of your symptoms? R

Completed By:

Date Completed: //

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□□/□□/□□□□

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40i. In the last 2 months, how much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the **hospital outpatient clinic** since the onset of your symptoms? R □□□□

HOSPITAL INPATIENT

41. In the last 2 months, how many times have you been admitted to hospital as an **inpatient** for TB treatment/ current symptoms? □□

If 00, go to question 42.

41a. What is the main mode of transport taken on your last visit to your usual **inpatient** department? □

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

41b. What is the distance from your usual residence to your usual hospital inpatient clinic? □

- 1 = <= 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

41c. What was the total cost of transportation (round trip) when you last visited your usual hospital **inpatient** clinic? (**Enter 000 if no cost.**) R □□□

41d. How much time did you spend in total travelling to and from your usual hospital **inpatient** clinic on your last visit? (HH:MM) □□:□□

41e. In the last 2 months, how many **nights** did you spend in the hospital **inpatient** clinic in total since the onset of your symptoms? □□

41f. In total (add all days from all friends/relatives), how many **days** did your friends and relatives accompany you while you were an **inpatient** at the hospital? □□□

41g. In the last 2 months, how much have you spent on medicines or other consumables in total (for all visits) at the **inpatient** clinic since the onset of your symptoms? R □□□□

41h. In the last 2 months, how much have you spent on admission and consultation fees in total (for all visits) at the **inpatient** clinic since the onset of your symptoms? R □□□□

41i. In the last 2 months, how much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the **inpatient** clinic since the onset of your symptoms? R □□□□

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41j. In the last 2 months, how much have you spent on food and other costs in total (for all visits) at the **inpatient** clinic since the onset of your symptoms? R

TRADITIONAL HEALER

42. In the last 2 months, how many times have you visited a **traditional healer** as a result of your TB treatment/current symptoms?

If 00, go to question 43.

42a. What is the main mode of transport taken on your last visit to your usual **traditional healer**?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

42b. What is the distance from your usual residence to your usual **traditional healer**?

- 1 = ≤ 2 kms
- 2 = 2-5 kms
- 3 = 5-10 kms
- 4 = > 10 kms

42c. What was the total cost of transportation (round trip) when you last visited your usual **traditional healer**?

(Enter 000 if no cost.) R

42d. How much time did you spend in total travelling to and from the **traditional healer** on your last visit for TB treatment/current symptoms? (HH:MM) :

42e. How much time did you spend with the **traditional healer** on your last visit? (HH:MM) :

42f. How many adults accompanied on your last visit to your usual **traditional healer**?.....

If 0, go to question 42g.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

42fi. Adult 1 main occupation:	42fii. Adult 2 main occupation:	42fiii. Adult 3 main occupation:	42fiv. Adult 4 main occupation:	42fv. Adult 5 main occupation:
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:



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- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

42g. In the last 2 months, how much have you spent on consultation fees in total (for all visits) at the **traditional healer** since the onset of your symptoms? R

OTHER

43. In the last 2 months, how much have you spent on supplements to your diet because of your symptoms, i.e. vitamins, meat, energy drinks, soft drinks, fruit, or medicines? (**Enter 0000 if you spent nothing on dietary supplements.**) R

44. In the last 2 months, have you been given a prescription at the public clinic to take to the private pharmacy to purchase TB-related medicines or other medical items? 1=Yes, 0=No
If No, go to question 45.

44a. In the last 2 months, how much have you spent on these items? R

44b. Did you pay for these items using your medical aid? 1=Yes, 0=No
If No, go to question 45.

44c. In the last 2 months, what is the estimated value of these products bought on your medical aid?
..... R

INCOME DURING TREATMENT

Please provide us with an estimate of your average days worked and cash income per month when you started treatment.

45. In the last two months, were you employed by government (two months ago)? 1=Yes, 0=No
If No, go to question 46.

45a. Days worked/month (government):

45b. Income/month (government): R

45c. In the last 2 months, how many work days have you lost due your TB illness (government)?

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45d. In the last 2 months, how much income have you lost due your TB illness (government)?

R

46. In the last two months, were you employed by private for profit sector? 1=Yes, 0=No

If No, go to question 47.

46a. Days worked/month (private for profit sector):

46b. Income/month (private for profit sector): R

46c. In the last 2 months, how many work days have you lost due to your TB illness

(private for profit sector)?

46d. In the last 2 months, how much income have you lost due to your TB illness

(private for profit sector)? R

47. In the last two months, were you employed by an NGO? 1=Yes, 0=No

If No, go to question 48.

47a. Days worked/month (NGO):

47b. Income/month (NGO): R

47c. In the last 2 months, how many work days have you lost due to your TB illness (NGO):

47d. In the last 2 months, how much income have you lost due to your TB illness (NGO): R

48. In the last two months, were you self-employed (merchant), business with employees? 1=Yes, 0=No

If No, go to question 49.

48a. Days worked/month (self-employed w/employees):.....

48b. Income/month (self-employed w/employees): R

48c. In the last 2 months, how many work days have you lost due to your TB illness (self-employed

w/employees):.....

48d. In the last 2 months, how much income have you lost due to your TB illness

(self-employed w/employees):..... R



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49. In the last two months, were you self-employed (merchant), business no employees?1=Yes, 0=No
If No, go to question 50.

49a. Days worked/month (self-employed no employees):

49b. Income/month (self-employed no employees):..... R

49c. In the last 2 months, how many work days have you lost due to your TB illness (self-employed no employees):

49d. In the last 2 months, how much income have you lost due to your TB illness (self-employed no employees): R

50. In the last two months, were you self-employed/ from home, farmer/ fishing/ agriculture?1=Yes, 0=No
If No, go to question 51.

50a. Days worked/month (self-employed from home):

50b. Income/month (self-employed from home): R

50c. In the last 2 months, how many work days have you lost due to your TB illness (self-employed from home):

50d. In the last 2 months, how much income have you lost due to your TB illness (self-employed from home): R

51. In the last two months, were you a daily labourer?1=Yes, 0=No
If No, go to question 52.

51a. Days worked/month (daily labour):

51b. Income/month (daily labour): R

51c. In the last 2 months, how many work days have you lost due to your TB illness (daily labour):

51d. In the last 2 months, how much income have you lost due your TB illness (daily labour): R

52. In the last two months, have you had any other form of employment?1=Yes, 0=No
If No, go to question 53.

52a. Days worked/month (other):

52b. Income/month (other): R

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52c. In the last 2 months, how many work days have you lost due to your TB illness (other): □□

52d. In the last 2 months, how much income have you lost due to your TB illness (other): ... R □□□□□□

53. In the last two months, have you been retired?..... 1=Yes, 0=No □

If No, go to question 54.

53a. What is your monthly pension?..... R □□□□□□

54. In the last two months, were you disabled/sick (in addition to your TB illness)? 1=Yes, 0=No □

55. In the last two months, did you receive any of the following sick/disability grants? 1=Yes, 0=No □

If No, go to question 56.

55a. Disability grant:..... 1=Yes, 0=No □

55b. HIV grant: 1=Yes, 0=No □

55c. Child grant: 1=Yes, 0=No □

55d. Other: 1=Yes, 0=No □

55di. If Other, specify: _____

55e. What is the total income from these grants?..... R □□□□□□

56. In the last two months, did you receive any non-monetary payments for your work? 1=Yes, 0=No □

If No, go to question 57.

56a. What do you estimate is the total value of the non-monetary payments you receive on average in a month? R □□□□□□

56b. In the last two months, have you received less non-monetary payments due to a reduction in working hours because of your TB illness? 1=Yes, 0=No □

If No, go to question 57.

56c. What is the estimated monetary value of the loss of non-monetary payments you would have received (last two months)? R □□□□□□

57. In the last two months, have you received any benefits or charitable donations in addition to your disability grant(s)? 1=Yes, 0=No □

If No, go to question 58.

Completed By: □□

Date Completed: □□/□□/□□□□

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57a. What is the estimated monetary value of these benefits or charitable donations, etc. you have received?

..... R □□□□□

58. In the last two months, when you are unable to work at your job, was anyone else in your household able to

take over your job-related tasks? 1=Yes, 0=No □

If No, go to question 59.

58a. In what category are these job-related tasks? □□

- | | |
|-------------------------------------------------------------|----------------------------------|
| 01 = Employed by government | 07 = Unemployed/looking for work |
| 02 = Employed by private for profit sector | 08 = Retired |
| 03 = Employed by NGO | 09 = Pupil/student |
| 04 = Self-employed (merchant), business with employees | 10 = Disabled/sick |
| 05 = Self-employed (merchant), business no employees | 11 = House maker |
| 06 = Self-employed/ from home, farmer/ fishing/ agriculture | 12 = Daily labourer |
| | 99 = Other, specify: |

59. In the last two months, how many hours had to be covered by members of your household because you were

unable to do your job-related tasks? □□□

If 00, go to question 60.

59a. What is the main occupation of the person who is covering your job-related tasks for you? □□

- | | |
|-------------------------------------------------------------|----------------------------------|
| 01 = Employed by government | 07 = Unemployed/looking for work |
| 02 = Employed by private for profit sector | 08 = Retired |
| 03 = Employed by NGO | 09 = Pupil/student |
| 04 = Self-employed (merchant), business with employees | 10 = Disabled/sick |
| 05 = Self-employed (merchant), business no employees | 11 = House maker |
| 06 = Self-employed/ from home, farmer/ fishing/ agriculture | 12 = Daily labourer |
| | 99 = Other, specify: |

60. When you are unable to work, is anyone else in your household able to take over your household-related tasks?

If No, go to question 61. 1=Yes, 0=No □

60a. In the last two months, how many hours had to be covered because you were unable to do your

household tasks? □□□

If 00, go to question 61.

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60b. What is the main occupation of the person who covering your household tasks? □□

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify:

61. Has anyone in your household had to care for you because of your TB illness? 1=Yes, 0=No □

If No, go to question 62.

61a. In the last two months, how many hours did this person have to care for you? □□□

If 00, go to question 62.

61b. What is the main occupation of the person who cared for you? □□

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify:

62. In the last two months, did you have to sell anything to pay for your TB treatment or to cover for your loss of income due to your TB illness? 1=Yes, 0=No □

If No, go to question 63.

62a. What was the value of the sold goods?..... R □□□□□

63. In the last 2 months, did you have to borrow any money as a result of income losses associated with your TB illness? 1=Yes, 0=No □

If NO, STOP, form is complete.

63a. How much did you have to borrow? R □□□□□

63b. How much in total do you have to pay back? R □□□□□

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PROTOCOL NUMBER: AUR2-8-103

TITLE: XTEND STUDY

XPRT MTB/RIF FOR DIAGNOSIS OF TUBERCULOSIS: EVALUATING
IMPACT AND COST-EFFECTIVENESS IN THE ROUTINE ROLL-OUT IN SOUTH
AFRICA

DATA COLLECTION INSTRUCTIONS: SUPPLEMENT 3

SS002: TB PATIENTS FOLLOW-UP 5-MOS INTERVIEW

1. Complete this paper CRF for all TB Patients who enrolled at 2 months from starting their treatment and are now at 5 months from starting their treatment. TB patients **cannot** already have participated in the Xtend TB Suspects cohort; but Exit Interviewees are eligible.
2. The TB Patient interview is completed with the TB Patient.
3. Ask each question in the order it appears on the form and choose the *best possible response* from the options provided.
4. Do not skip questions unless told to do so by the skip logic.
5. Do not mark outside of the designated response areas. Do not write notes or make marks in the margins.
6. If you make a mistake, refer to the Data Collection instructions for 'Correcting CRFs'.
7. After the interview is complete review the form to ensure all questions were answered **before ending the interview with the participant**.



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4b. Since we last interviewed you, how many visits have you made to this clinic to collect TB treatment? [] []

5. What is your **current** treatment regimen: []

- 1 = Pills only
- 2 = Pills plus injection
- 3 = MDR TB Treatment
- 4 = Don't know
- 9 = Other, specify: _____

OTHER PUBLIC HEALTH CLINIC

6. Have you had to visit a **different public clinic** as a result of your TB treatment symptoms? 1=Yes, 0=No []

If No, go to question 8.

7. In the last month, how many times have you visited this **other** public clinic as a result of your TB treatment symptoms? [] []

7a. What is the main mode of transport taken on your last visit to this **other** public clinic? []

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

7b. What was the total cost of transportation (round trip) when you last visited this **other** public clinic? **(Enter 000 if no cost.)** R [] [] []

7c. How much time in total did you spend travelling (round trip) when you last visited the **other** public clinic? (HH:MM) [] [] : [] []

7d. How much time did you spend in the **other** public clinic on your last visit for TB treatment symptoms? (HH:MM) [] [] : [] []

7e. How many adults accompanied you to the **other** public clinic on your last visit for TB treatment symptoms? [] **If 0, go to question 8.**

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For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

7ei. Adult 1 main occupation:	7eii. Adult 2 main occupation:	7eiii. Adult 3 main occupation:	7eiv. Adult 4 main occupation:	7ev. Adult 5 main occupation:
[] []	[] []	[] []	[] []	[] []
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

PHARMACY

8. In the last month, how many times have you had to visit a **private pharmacy** as a result of your TB treatment

symptoms? [] []

If 00, go to question 9.

8a. What is the main mode of transport taken on your last visit to your usual **private pharmacy**? []

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

8b. What was the total cost of transportation (round trip) when you last visited your usual **private pharmacy**?

(Enter 000 if no cost.).....R [] [] []

8c. How much time in total did you spend travelling (round trip) when you last visited your usual **private pharmacy**?

.....(HH:MM) [] [] : [] []

8d. How much time did you spend in the **private pharmacy** on your last visit for TB treatment symptoms?

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.....(HH:MM) [] [] : [] []

8e. How many adults accompanied you to your usual **private pharmacy** on your last visit for TB treatment

symptoms? []

If 0, go to question 8f.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

8ei. Adult 1 main occupation:	8eii. Adult 2 main occupation:	8eiii. Adult 3 main occupation:	8eiv. Adult 4 main occupation:	8ev. Adult 5 main occupation:
[] []	[] []	[] []	[] []	[] []
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

8f. In the last month, how much have you spent on medicine or other consumables related to your TB treatment

symptoms in total (for all visits) at the private pharmacy? R [] [] [] []

8g. Did you pay for these medicines using your medical aid? 1=Yes, 0=No []

GENERAL PRACTITIONER

9. In the last month, how many times have you visited a **general practitioner (GP)** as a result of your TB treatment

symptoms? [] []

If 00, go to question 10.

9a. What is the main mode of transport taken on your last visit to your usual **GP**? []

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

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9b. What was the total cost of transportation (round trip) when you last visited your usual GP? R
(Enter 000 if no cost.)

9c. How much time in total did you spend travelling (round trip) when you last visited your usual GP?
..... (HH:MM) :

9d. How much time did you spend at your usual GP on your last visit? (HH:MM) :

9e. How many adults accompanied you to your usual GP on your last visit?
If 0, go to question 9g.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

9ei. Adult 1 main occupation:	9eii. Adult 2 main occupation:	9eiii. Adult 3 main occupation:	9eiv. Adult 4 main occupation:	9ev. Adult 5 main occupation:
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

9f. In the last month, how much have you spent on medications or other consumables in total (for all visits) at your usual GP? R

9g. In the last month, how much have you spent on consultation fees in total (for all visits) at your usual GP? R

9h. In the last month, how much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the GP? R

9i. Did you pay using your medical aid? 1=Yes, 0=No

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HOSPITAL OUTPATIENT CLINIC

10. In the last month, how many times have you had to visit a **hospital outpatient clinic** as a result of your TB treatment symptoms?.....

If 00, go to question 11.

10a. What is the main mode of transport taken on your last visit to your usual **hospital outpatient clinic** for TB treatment?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

10b. What was the total cost of transportation (round trip) when you last visited your usual **hospital outpatient clinic**? (*Enter 000 if no cost.*) R

10c. How much time in total did you spend travelling (round trip) when you last visited your usual **hospital outpatient clinic**? HH:MM) :

10d. How much time did you spend in the **hospital outpatient clinic** on your last visit? .. (HH:MM) :

10e. How many adults accompanied you to your usual **hospital outpatient clinic** on your last visit for TB treatment?

If 0, go to question 10f.

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For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

Table with 5 columns for adult main occupations (10ei to 10ev) and rows for occupation codes and 'If other, specify'.

- 01 = Employed by government
02 = Employed by private for profit sector
03 = Employed by NGO
04 = Self-employed (merchant), business with employees
05 = Self-employed (merchant), business no employees
06 = Self-employed/ from home, farmer/ fishing/ agriculture

- 07 = Unemployed/looking for work
08 = Retired
09 = Pupil/student
10 = Disabled/sick
11 = House maker
12 = Daily labourer
99 = Other, specify

10f. In the last month, how much have you spent on medications or other consumables in total (for all visits) at the hospital outpatient clinic related to your TB treatment? R □□□□

10g. In the last month, how much have you spent on consultation fees in total (for all visits) at the hospital outpatient clinic related to your TB treatment? R □□□□

10h. In the last month, how much have you spent on diagnostic costs (including X-rays) in total (for all visits) at the hospital outpatient clinic related to your TB treatment? R □□□□

HOSPITAL INPATIENT

11. Since we last interviewed you, how many times have you been admitted to hospital as an inpatient for TB treatment? □□

If 00, go to question 12.

11a. What is the main mode of transport taken on your each visit to your usual inpatient department? □

- 1 = Walk
2 = Bike
3 = Bus/taxi
4 = Car
5 = Train
9 = Other, specify: _____

Completed By: □□

Date Completed: □□/□□/□□□□

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11b. What was the total cost of transportation (round trip) for each of these visits to your usual hospital

inpatient clinic? *(Enter 000 if no cost.)* R

11c. How much time did you spend in total travelling to and from your usual hospital **inpatient** clinic on your

each visit? (HH:MM) :

11d. Since we last interviewed you, for how many **nights** were you admitted to hospital in total?

11e. In total (add all days from all friends/relatives), how many **days** did your friends and relatives accompany

you while you were an **inpatient** at the hospital?

11f. Since we last interviewed you, how much have you spent on medicines or other consumables in total (for

all visits) at the **inpatient** clinic? R

11g. Since we last interviewed you, how much have you spent on admission and consultation fees in total (for

all visits) at the **inpatient** clinic? R

11h. Since we last interviewed you, how much have you spent on diagnostic costs (including X-rays) in total (for

all visits) at the **inpatient** clinic? R

11i. Since we last interviewed you, how much have you spent on food and other costs in total (for all visits) at

the **inpatient** clinic? R

TRADITIONAL HEALTH PRACTITIONER

12. In the last month, how many times have you visited a **traditional health practitioner** as a result of your TB

treatment symptoms?

If 00, go to question 13.

12a. What is the main mode of transport taken on your last visit to your usual **traditional health practitioner**?

- 1 = Walk
- 2 = Bike
- 3 = Bus/taxi
- 4 = Car
- 5 = Train
- 9 = Other, specify: _____

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12b. What was the total cost of transportation (round trip) when you last visited your usual **traditional health practitioner?** (Enter 000 if no cost.) R

12c. How much time did you spend in total travelling to and from the **traditional health practitioner** on your last visit for TB treatment? (HH:MM) :

12d. How much time did you spend with the **traditional health practitioner** on your last visit? (HH:MM) :

12e. How many adults accompanied on your last visit to your usual **traditional health practitioner?**
If 0, go to question 12g.

For each adult accompanied, complete main occupation category and specify if necessary using the code list below.

12ei. Adult 1 main occupation:	12eii. Adult 2 main occupation:	12eiii. Adult 3 main occupation:	12eiv. Adult 4 main occupation:	12ev. Adult 5 main occupation:
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
If other, specify:	If other, specify:	If other, specify:	If other, specify:	If other, specify:

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker
- 12 = Daily labourer
- 99 = Other, specify

12f. In the last month, how much have you spent on consultation fees in total (for all visits) at the **traditional health practitioner?** R

OTHER

13. In the last month, how much have you spent on supplements to your diet because of your TB treatment, i.e. vitamins, meat, energy drinks, soft drinks, fruit, or medicines? (Enter 0000 if you spent nothing on dietary supplements.) R

14. In the last month, have you been given a prescription at the public clinic to take to the private pharmacy to purchase TB-related medicines or other medical items? 1=Yes, 0=No
If No, go to question 15.

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14a. In the last month, how much have you spent on these items? R

14b. Did you pay for these items using your medical aid? 1=Yes, 0=No

If No, go to question 15.

14c. In the last month, what is the estimated value of these products bought on your medical aid?
..... R

INCOME DURING TREATMENT

Please provide us with an estimate of your average days worked and cash income per month when you started treatment.

15. In the last month, were you employed by government? 1=Yes, 0=No

If No, go to question 16.

15a. Days worked per month (government):

15b. Income per month (government): R

15c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No

If No, go to question 16.

15d. Has your income increased or decreased?..... 1=Increased, 2= Decreased

15e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

15f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (government)?..... R

16. In the last month, were you employed by private for profit sector? 1=Yes, 0=No

If No, go to question 17.

16a. Days worked per month (private for profit sector):

16b. Income per month (private for profit sector): R

16c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No

If No, go to question 17.

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16d. Has your income increased or decreased?.....1=Increased, 2= Decreased []

16e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

16f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (private for profit)?..... R [] [] [] [] []

17. In the last month, were you employed by an NGO? 1=Yes, 0=No []

If No, go to question 18.

17a. Days worked per month (NGO): [] []

17b. Income per month (NGO): R [] [] [] [] []

17c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No []

If No, go to question 18.

17d. Has your income increased or decreased?.....1=Increased, 2= Decreased []

17e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

17f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (NGO)?..... R [] [] [] [] []

18. In the last month, were you self-employed (merchant), business with employees? 1=Yes, 0=No []

If No, go to question 19.

18a. Days worked per month (self-employed w/employees): [] []

18b. Income per month (self-employed w/employees):..... R [] [] [] [] []

18c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No []

If No, go to question 19.

18d. Has your income increased or decreased?.....1=Increased, 2= Decreased []



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18e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

18f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (self-employed w/employees)?..... R □□□□□

19. In the last month, were you self-employed (merchant), business no employees? 1=Yes, 0=No □

If No, go to question 20.

19a. Days worked per month (self-employed no employees): □□

19b. Income per month (self-employed no employees): R □□□□□

19c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No □

If No, go to question 20.

19d. Has your income increased or decreased?.....1=Increased, 2= Decreased □

19e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

19f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (self-employed no employees)?..... R □□□□□

20. In the last month, were you self-employed/ from home, farmer/ fishing/ agriculture?1=Yes, 0=No □

If No, go to question 21.

20a. Days worked per month (self-employed from home): □□

20b. Income per month (self-employed from home): R □□□□□

20c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No □

If No, go to question 21.

20d. Has your income increased or decreased?.....1=Increased, 2= Decreased □



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20e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

20f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (self-employed from home)?..... R □□□□□

21. In the last month, were you a doing piece work? 1=Yes, 0=No □
If No, go to question 22.

21a. Days worked per month (piece work): □□

21b. Income per month (piece work):..... R □□□□□□

21c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No □
If No, go to question 22.

21d. Has your income increased or decreased?..... 1=Increased, 2= Decreased □

21e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness

21f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (piece work)?..... R □□□□□

22. In the last month, have you had any other form of employment?..... 1=Yes, 0=No □
If No, go to question 23.

22a. Days worked per month (other): □□

22b. Income per month (other):..... R □□□□□□

22c. Has your income changed since we last interviewed you?..... 1=Yes, 0=No □
If No, go to question 23.

22d. Has your income increased or decreased?..... 1=Increased, 2= Decreased □

22e. Was this change due to:

1 = Feeling better, 2 = Feeling worse, 3 = Less time to receive TB treatment (less often, closer to home), 4 = More time to receive TB treatment (more often, further from home or work), 5 = Other circumstance not to do with TB illness



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22f. Since we last interviewed you, many work days have you lost due to your TB illness (including collecting TB treatment) (other)?..... R □□□□□

23. Since we last interviewed you, have you been receiving a retirement pension? 1=Yes, 0=No □
If No, go to question 24.

23a. Has this started since we last interviewed you? 1=Yes, 0=No □
If No, go to question 24.

If yes, when did it start?

23b. What is your monthly pension? R □□□□□

24. In the last month, were you disabled/sick (in addition to your TB illness)? 1=Yes, 0=No □

25. In the last month, did you receive any of the following sick/disability grants?..... 1=Yes, 0=No □
If No, go to question 26.

25a. Disability grant:..... 1=Yes, 0=No □

25b. HIV grant: 1=Yes, 0=No □

25c. Child grant: 1=Yes, 0=No □

25d. Other: 1=Yes, 0=No □

25di. If Other, specify: _____

25e. What was your total income from these grants in the last month?..... R □□□□□

25f. Has this amount changed since we last interviewed you?..... 1=Yes, 0=No □
If No, go to question 26.

25g. Has it increased or decreased?..... 1 = Increased, 0 = Decreased

25h. Did this change due to TB illness or other unrelated circumstances?

26. In the last month, did you receive any non-monetary payments for your work? 1=Yes, 0=No □
If No, go to question 27.

26a. What do you estimate is the total value of the non-monetary payments in the last month? R □□□□□

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26b. Has this amount changed since we last interviewed you?.....1=Yes, 0=No

If No, go to question 27.

26c. Has it increased or decreased?..... 1 = Increased, 0 = Decreased

26d. Did this change due to TB illness or other unrelated circumstances?

27. In the last month, have you received less non-monetary payments due to a reduction in working hours

because of your TB illness?1=Yes, 0=No

If No, go to question 28.

27a. What is the estimated monetary value of the loss of non-monetary payments in the last month? R

28. In the last month, have you received any benefits or charitable donations in addition to your disability grant(s)?

1=Yes, 0=No

If No, go to question 29.

28a. What is the estimated monetary value of these benefits or charitable donations, etc. you have received in the last month?

..... R

28b. Has this amount changed since we last interviewed you?.....1=Yes, 0=No

If No, go to question 26.

28c. Has it increased or decreased?..... 1 = Increased, 0 = Decreased

28d. Did this change due to TB illness or other unrelated circumstances?

29. In the last month, when you are unable to work at your job, was anyone else in your household able to take

over your job-related tasks?1=Yes, 0=No

If No, go to question 30.

29a. In what category are these job-related tasks?

- 01 = Employed by government
- 02 = Employed by private for profit sector
- 03 = Employed by NGO
- 04 = Self-employed (merchant), business with employees
- 05 = Self-employed (merchant), business no employees
- 06 = Self-employed/ from home, farmer/ fishing/ agriculture
- 07 = Unemployed/looking for work
- 08 = Retired
- 09 = Pupil/student
- 10 = Disabled/sick
- 11 = House maker

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12 = Daily labourer
99 = Other, specify: _____

30. In the last month, how many hours had to be covered by members of your household because you were

unable to do your job-related tasks?..... □□□

If 00, go to question 31.

30a. What is the main occupation of the person who is covering your job-related tasks for you? □□

- | | |
|-------------------------------------------------------------|----------------------------------|
| 01 = Employed by government | 07 = Unemployed/looking for work |
| 02 = Employed by private for profit sector | 08 = Retired |
| 03 = Employed by NGO | 09 = Pupil/student |
| 04 = Self-employed (merchant), business with employees | 10 = Disabled/sick |
| 05 = Self-employed (merchant), business no employees | 11 = House maker |
| 06 = Self-employed/ from home, farmer/ fishing/ agriculture | 12 = Daily labourer |
| | 99 = Other, specify: _____ |

31. When you are unable to work, is anyone else in your household able to take over your household-related tasks?

If No, go to question 32. 1=Yes, 0=No □

31a. In the last month, how many hours had to be covered because you were unable to do your household

tasks?..... □□□

31b. What is the main occupation of the person who covering your household tasks? □□

- | | |
|-------------------------------------------------------------|----------------------------------|
| 01 = Employed by government | 07 = Unemployed/looking for work |
| 02 = Employed by private for profit sector | 08 = Retired |
| 03 = Employed by NGO | 09 = Pupil/student |
| 04 = Self-employed (merchant), business with employees | 10 = Disabled/sick |
| 05 = Self-employed (merchant), business no employees | 11 = House maker |
| 06 = Self-employed/ from home, farmer/ fishing/ agriculture | 12 = Daily labourer |
| | 99 = Other, specify: _____ |

32. Has anyone in your household had to care for you because of your TB illness? 1=Yes, 0=No □

If No, go to question 33.

32a. In the last month, how many hours did this person have to care for you?..... □□□

32b. What is the main occupation of the person who cared for you? □□

- | | |
|--------------------------------------------|--------------------------------------------------------|
| 01 = Employed by government | 04 = Self-employed (merchant), business with employees |
| 02 = Employed by private for profit sector | 05 = Self-employed (merchant), business no employees |
| 03 = Employed by NGO | |

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06 = Self-employed/ from home, farmer/ fishing/ agriculture

10 = Disabled/sick

11 = House maker

12 = Daily labourer

07 = Unemployed/looking for work

99 = Other, specify:

08 = Retired

09 = Pupil/student

33. In the last month, did you have to sell anything to pay for your TB treatment or to cover for your loss of income due to your TB illness? 1=Yes, 0=No

If No, go to question 34.

33a. What was the value of the sold goods?..... R

34. In the last month, did you have to borrow any money as a result of income losses associated with your TB illness? 1=Yes, 0=No

If NO, STOP, form is complete.

34a. How much did you have to borrow? R

34b. How much in total do you have to pay back? R

Thank you for your time and participation in the study [give the participant the airtime voucher]

Completed By:

Date Completed: