The economic cost and cost-effectiveness of treatment strategies and care models to reduce the burden of multi-drug resistant tuberculosis

Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy by Laura Rosu

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Abstract

Tuberculosis (TB) is one of the main causes of death in many low-middle-income countries (LMIC). It can exacerbate poverty, food insecurity and malnutrition and multi-faceted approaches are required to tackle the TB epidemic.

Multidrug-resistant tuberculosis (MDR-TB) is caused by TB bacteria that is resistant to at least isoniazid and rifampicin, the two most potent and widely used TB drugs. As the global TB incidence is falling at just 2% per year, new ways of addressing the disease must be found. Economic evaluation of alternative treatment strategies and care models is vital to inform policy and implementation, with the goal of maximising the impact on MDR-TB with available resources.

This thesis aimed to contribute to this goal by evaluating the cost-effectiveness of two new MDR-TB regimens and comparing the cost of alternative directly-observed treatment (DOT) approaches.

The work 1) showed that a 9-month injectable-containing regimen was cheaper and more effective than the standard-of-care (SOC) in 2011, when the trial began, 2) developed economic evaluation methods for use in the second trial phase, 3) showed that an alternative 9-month all-oral regimen is likely not cost-effective compared to the 9-month injectable-containing regimen (tested in the first phase and becoming the new SOC during the second phase) and that a 6-month regimen is likely to be cost-effective, 4) showed that patient-centred and hybrid DOT approaches are less costly than SOC, and also 5) proved that digital-DOT or family-observed DOT are also less costly than SOC for the short MDR-TB regimen.

The results of the first paper influenced World Health Organization (WHO) MDR-TB treatment guidelines, which in 2019 recommended the 9-month injectable-containing regimen, mentioning that the reduced cost of the shorter regimen to patients and the health services is expected to favour equity by freeing up resources to cover the care of more patients. The economic evaluation protocol informed the analysis of the second study whose results are published in paper 3. These results were also reviewed by WHO guideline development group. This work had unexpected findings: most previous modelling studies showed that the all-oral short regimen was likely to be cost-effective in all settings, while our study showed that this would not be true for most settings. These economic evaluation results should be used to guide the programmatic implementation of the short all-oral regimen.

Collectively, these studies showed that although MDR-TB treatment is free at the point of care, patients still spend large amounts of money for receiving care and with the majority experiencing catastrophic costs. Thus, as cost and efficacy data on alternative DOT approaches is lacking, two separate modelling approaches (one operational model and one decision tree) were used to compare the cost of patient-centred and digital DOT delivery models with SOC. Results showed that these strategies can reduce patient and health system costs without efficiency-cost trade-offs.

The results of our detailed economic analysis of the economic impact of MDR-TB on patients and their households suggested that effective clinical interventions alone need to be complemented with socioeconomic interventions to end TB.

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Abbreviations

95% CI	95% Confidence Interval
99DOTS	A low-cost approach for monitoring and improving tuberculosis medication adherence
APPG	All Party Parliamentary Group
BCG	bacilli Calmette-Guerin
CEAC	Cost-effectiveness acceptability curve
COVID	Coronavirus disease that emerged in 2019
DES	Discrete Event Simulation
DOT	Directly-observed therapy
DOTS	Directly-observed therapy shortcourse
DS-TB	Drug-sensitive tuberculosis
ECG	Electrocardiogram
GDF	Global Drug Facility
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
LMIC	Low-Middle Income Countries
LTFU	Lost to follow up- patients who do not complete treatment
MDR-TB	Multi-drug Resistant Tuberculosis
NTP	National Tuberculosis Programmes
Pre-XDR-TB	pre-extensively drug-resistant TB
QALY	Quality-Adjusted Life-Years
RR-TB	Rifampicin-Resistant Tuberculosis
SAE	Serious Adverse Event
SMS	Short Message Service
SOC	Standard Of Care
STREAM	Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drug for Patients with Multidrug-resistant Tuberculosis
TB	Tuberculosis
VOT	Video-observed treatment
WHO	World Health Organization
WTP	Willingness-to-pay threshold

Introduction

1. History of tuberculosis

Human tuberculosis (TB) is a global epidemic affecting mainly low-income populations. Recent genetic data showed that *Mycobacterium tuberculosis* complex in humans has been around for at least 15,000 years.[1] However, despite substantial research, the timing, cause and geographical origin of TB in humans is still under debate. Until 100 years ago, it was thought that bovines transmitted the *Mycobacterium* to humans as people started drinking milk or consuming its derivates (containing *Mycobacterium bovis*) from the domesticated animals during the agricultural revolution, in 8300-5500 BC.[2,3] Recent studies showed no relationship between *M. bovis* and *M. tuberculosis* as they have divergent evolutionary lineages.[2,3]

The infectious origin of TB was first mentioned in 1720 by Benjamin Marten, in a publication called 'A new theory of Consumption'.[4] It was first called 'tuberculosis' in the mid-19th century.[4] It soon became apparent that problematic social conditions were associated with the disease: in 1838-1839, a third of English tradesmen died of TB, compared to a sixth of the upper class.[4]

The isolation of the tubercle bacillus in 1882 by Robert Koch was a major discovery and a turning point in the understanding of the disease. Following this, the Mantoux tuberculin skin test, bacilli Calmette-Guerin (BCG) vaccination and streptomycin and other anti-TB drugs were discovered.[4]

More than 100 years later, TB is still a major public health problem, being the second leading infectious disease killer after COVID-19 since 2020.[5] Moreover, the only licensed vaccine for prevention of TB remained the BCG and is used to prevent severe forms of TB in children.

2. General tuberculosis characteristics

TB is spread through air when people with active TB expel TB bacteria through air droplets.[6] If the body fights the bacteria to stop it from growing it cannot evolve into active TB and remains as a latent infection. For more than 90% of people who have the latent TB infection, the bacteria remain inactive without causing TB disease in their lifetime.[7] However, for the others, especially those with a weaker immune system, the bacteria become active causing TB disease. People with human immunodeficiency virus (HIV), previous TB infection, and other diseases that make it hard for the body to fight the bacteria and those who have not been treated correctly for the TB infection in the past, have a higher chance of getting active TB disease.[6]

TB diagnosis has drastically improved over recent years. A few rapid molecular tests are now available and endorsed by World Health Organization (WHO), however, sputum smear microscopy (microscopic examination) is still widely used while sputum culture (inoculation onto culture media) remains the gold standard for TB diagnosis.[8] Once diagnosed, patients' treatment responses are monitored using smear or culture.[8]

TB usually affects the lungs (pulmonary TB), however TB that occurs in the organ system other than the lungs, known as extrapulmonary TB, can also occur. Main types of pulmonary TB are:

- Drug-susceptible TB (DS-TB)- active TB without evidence of infection with strains that are resistant to either rifampicin or isoniazid

- Rifampicin-resistant TB (RR-TB)- TB that is resistant to rifampicin, one of the most commonly used drugs to treat TB
- Multi-drug resistant TB (MDR-TB)- TB strain that is resistant to both rifampicin and isoniazid. MDR-TB and RR-TB are sometimes used interchangeable as isoniazid resistance is not usually tested for and the treatment is the same for both types of TB
- Pre-extra-drug resistant TB (pre-XDR-TB)- TB strain that is resistant to rifampicin (may also be resistant to isoniazid) and that is also resistant to any fluoroquinolone
- Extra-drug resistant TB (XDR-TB)- resistance to at least one additional drug from levofloxacin, moxifloxacin, bedaquiline or linezolid is also presented in addition to the resistance for pre-XDR-TB

The prognosis of untreated tuberculosis is difficult to study, as not treating patients once diagnosed with the disease is unethical. However, studies from the pre-chemotherapy era revealed that untreated HIV-negative patients have a 10-year case fatality rate of up to 86%.[9]

2.1 Multi-drug resistant tuberculosis

The occurrence of MDR-TB makes TB treatment more challenging and threaten efforts to end TB, as it is more difficult to treat than DS-TB.

Resistance to certain drugs has been observed since the use of the first anti-TB drug, streptomycin, when it became obvious that combining different drugs was key to prevent resistance. The most common risk factors for MDR-TB are the following[10]:

1) Defaulting DS-TB treatment. This can happen when patients do not take their full course of treatment or there are treatment interruptions. The root cause of these can be attributed to either the lack of support for patients who are in difficult socioeconomic situations, weaknesses in the health system (i.e. anti-TB drug stockouts) or poor treatment monitoring (non-adherence to the treatment and monitoring guidelines)
2) Relapse after a full course of treatment for a DS-TB regimen
3) Person-to-person transmission of MDR-TB strains through exposure to a known case
4) HIV coinfection

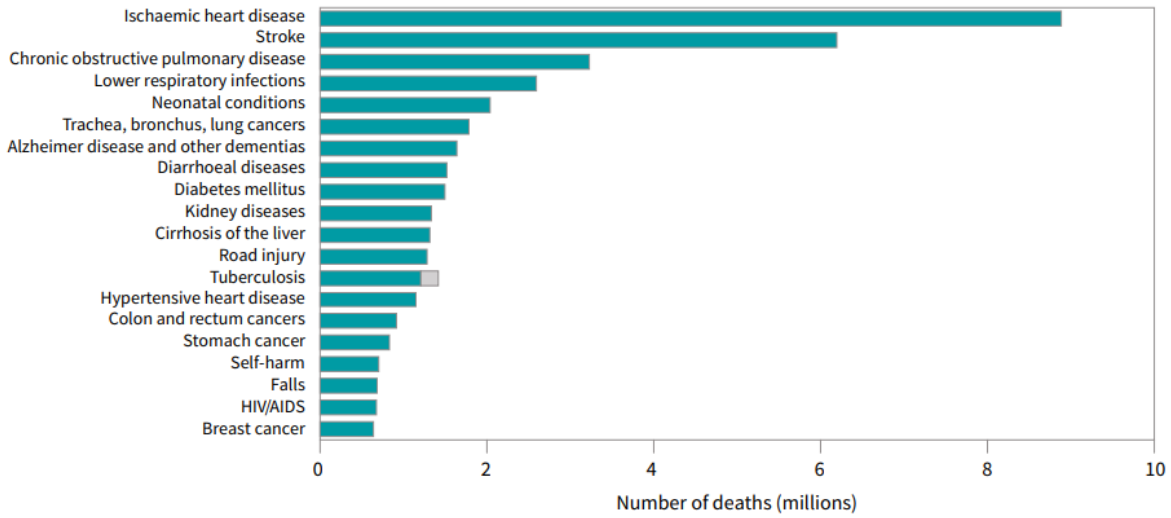
Studies[11,12] show that transmission of MDR strains account for most of the cases, with residential communities and related public facilities being the most common transmission setting. Prompt and effective treatment could therefore reduce MDR-TB transmission.

3. Current tuberculosis mortality, case notification and incidence

The coronavirus (COVID-19) pandemic had a damaging impact on the burden of TB disease. Progress made up to 2019 in tackling TB has slowed, stalled or reversed.[8]

In 2021 there were an estimated 1.6 million deaths due to TB, a 6% increase compared to 2020 and 12.5% compared to 2019, making TB the 13th leading cause of death worldwide (figure 1).[8]

Figure 1. Top causes of death worldwide in 2019

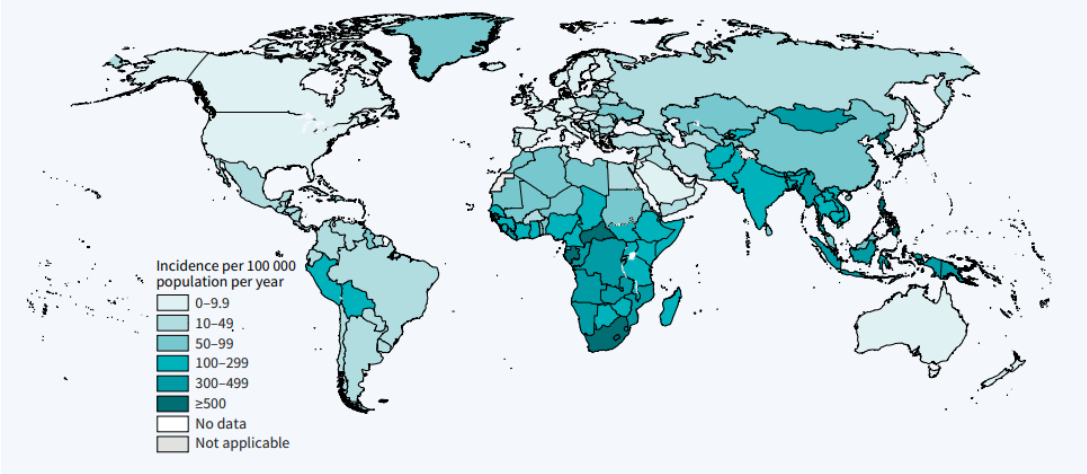


Source: WHO Global TB report, 2022[8]

Following large increases in case notification rates between 2017 and 2019, there was a reduction of 18% between 2019 and 2020, suggesting that the number of people with active TB and not on treatment has increased.[8]

In 2021 the TB incidence rate increased by 3.6% from the previous year, after declining by approximately 2% per year for most of the past 20 years (figure 2).[8]

[9]*Figure 2. Estimated TB incidence rates in 2021*



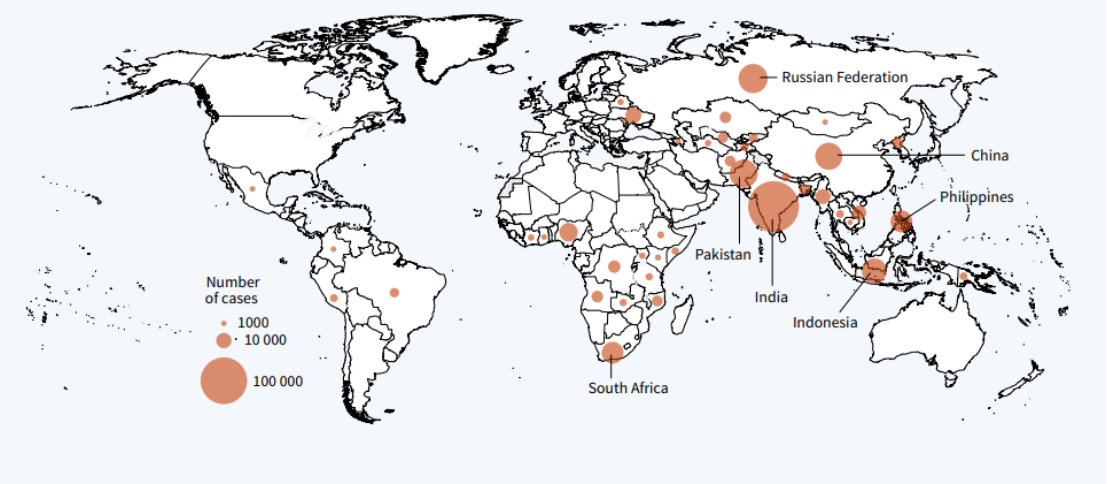
Source: WHO Global TB report 2022.[8]

Among all new TB cases, 3.6% of people had MDR/RR-TB and 18% of those previously treated. India, Russia and Pakistan accounted for 42% of global cases in 2021 (Figure 3).[8]

Modelling suggests that TB incidence and mortality will continue to increase in future, but this modelling did not account for the worsening trends on the TB determinants: average income and prevalence of

undernourishment.[8] This could have further knock on effects on number of people developing TB following an *M. tuberculosis* infection. Lower incomes might also delay care seeking behaviour with effects for transmission and outcomes.

Figure 3. Estimated incidence of MDR/RR-TB in 2021, for countries with at least 1000 incident cases. The seven highest MDR/RR-TB burden countries are labelled.



Source: WHO Global TB report 2022[8]

4. Global strategies to end the tuberculosis epidemic

The first WHO TB-focussed global strategy was launched in 1994. The 1994 DOTS (Directly Observed Treatment, Short-course) strategy recommended that countries focussed on strengthening five key components to address TB: political commitment; microscopy services; drug supplies; surveillance and monitoring systems; and, use of standardised regimens and directly-observed treatment (DOT).[13] It was followed by the 2006 'STOP TB' strategy. Its main objectives were to achieve universal access to high-quality diagnosis and patient-centred treatment, reduce the socioeconomic burden from TB, as well as protect vulnerable and poor populations from TB[14]. STOP TB also aimed to address the emerging challenges of HIV-associated TB and MDR-TB and improve access to TB care by strengthening health systems.

In 2015, WHO launched the 'End TB' Strategy which called for intensive multi-partner (ministries of health in collaboration with all stakeholders, including communities, civil society and private sector) multi-sectoral actions (biomedical, public health, socioeconomic interventions, research and innovation) to end TB.[15] The strategy builds on three strategic pillars: (i) integrated, patient-centred care and prevention, (ii) bold policies and supportive systems and (iii) intensified research and innovation. The success of the strategy is measured through the three 2035 indicators in table 1. Key components of the strategy include reducing poverty, universal healthcare and elimination of catastrophic costs due to TB. Catastrophic costs are defined as the total patient cost related to TB exceeding 20% of the annual pre-TB household income.[16]

Table 1. End TB strategy milestones and targets compared to 2015 numbers

	Milestones		Targets	
	2020	2025	2030	2035
Reduction in number of TB deaths (%)	35%	75%	90%	95%
Reduction in TB incidence rate	20%	50%	80%	90%
Families facing catastrophic costs due to TB	0%	0%	0%	0%

The 2020 milestones have not been achieved in most countries, and due to the COVID-19 pandemic many countries are further away in 2021 than they were in 2019.[8] In 2021, the number of TB deaths and incidence reduced by 5.9% and 10.0%, respectively since 2015; these reductions are way below the milestones above. Moreover, in 2021, close to one in two TB-affected households faced costs higher than 20% of their household income, so the milestone of 0% families facing catastrophic costs as a result of TB was also not achieved.[8]

Traditionally, in-person DOT is a key component of the WHO global strategies to end TB. It is an approach used to support patients undergoing TB treatment that ensures adherence to treatment and maximise its efficacy, by observing TB patients swallowing their pills. WHO recommends this to be provided in the context of patient-centred care[17] and based on the individual's needs, acceptability, and preferences. Also, part of the End TB Strategy Pillar 1, patient-centred care can have significant benefits to TB patients as the individual's rights and welfare are also considered when treatment decisions are taken. The treatment adherence interventions promoted by patient-centred care are: patient education, communication (through home visits, digital medication monitors, etc.), material support (food, food vouchers, transport vouchers, housing incentives, etc.), psychological support and staff education (educational tools for reminders).[18] Therefore, WHO supports DOT delivered by a health-care worker or a community member in different settings: at home, at work, in the community or at a health facility. Digital DOT, such as SMS, 99DOTS or VOT are also considered patient-centred treatment administration options.[19]

5. Tuberculosis treatment regimens

The WHO treatment guidelines play an important role in supporting countries to achieve the End TB Strategy. While treatment for DS-TB has remained largely unchanged, the MDR-TB treatment landscape has evolved considerably over the past 10 years as reflected in the evolving WHO treatment guidelines (table 2). In designing the guidelines, WHO uses mainly clinical trial and observational studies data. The latest DS-TB guidelines recommend, with a high certainty of evidence, that new patients with pulmonary DS-TB should receive an intensive phase of treatment of two months and a continuation phase of four months. When implementing the DS-TB regimen it is very important for the NTPs to ensure adequate supervision of rifampicin, for the whole treatment duration, to avoid MDR/RR-TB. Historically, WHO treatment recommendations for MDR-TB have been based on very low certainty of evidence due to the lack of relevant clinical trials, leading to calls for additional high-quality evidence.

Table 2. Summary of WHO guidelines, policies, and statements on the treatment of MDR-TB and key STREAM events

Date of publication	WHO document/Key event	What changed
2011	Guidelines for the programmatic management of MDR-TB. 2011 update	Introduction of longer, injectable-containing regimens
2013	The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Interim policy guidance	
2014	The use of delamanid in the treatment of MDR-TB: Interim policy guidance	
2016	WHO treatment guidelines for DR-TB. 2016 update, May	
2016	WHO treatment guidelines for DR-TB. 2016 update. October revision	Introduction of shorter, injectable-containing regimens based on very low evidence
2016	The use of delamanid in the treatment of MDR-TB in children and adolescents: Interim policy guidance	
2018	WHO position statement on the use of delamanid for MDR-TB	
2018	WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for DR-TB	
2018	Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results	
2018	Rapid Communications: Key changes to treatment of MDR and RR TB	Introduction of shorter, injectable-containing regimens
2018	WHO treatment guidelines for MDR/RR-TB. 2018 update. Pre-final text	
2019	WHO consolidated guidelines on MDR-TB	Introduction of longer, all-oral regimens
2020	WHO consolidated guidelines on TB. Module 4: treatment- DR-TB treatment	Introduction of shorter, all-oral regimens
2022	WHO consolidated guidelines on TB. Module 4: treatment- DR-TB treatment. 2022 update, December	Introduction of 6-month all-oral regimens

5.1 The STREAM trial

Directly addressing public calls for data on MDR-TB treatments, STREAM (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drug for Patients with Multidrug-resistant Tuberculosis) was the largest recruited clinical trial, multi-country and first to examine shortened regimens for MDR-TB (table 3). The STREAM trial is comprised of two stages. Stage 1 started in 2012 and was a pragmatic clinical trial. Treatments evaluated in Stage 1 were the locally-used MDR-TB regimens in accordance with the 2011 WHO MDR-TB treatment guidelines[20] (regimen A, a 20-22 month regimen) and the regimen first described by Van Deun, the so-called 'Bangladeshi regimen'[21] (regimen B, a 9-month

regimen), both injectable-containing regimens (see table 4 for dosages and drugs included in regimen B).[22] Clinical results showed that favourable status was achieved in 79.8% participants in regimen A and in 78.8% of those in regimen B and proved that regimen B is non-inferior to regimen A.

Following a review of the STREAM data, the WHO released in 2018 a position statement[23] on the use of the shorter MDR-TB regimen tested in STREAM, which was followed by a rapid communication on the key changes to treatment of MDR-TB[24]. Although shortening treatment duration represented a massive improvement in MDR-TB treatment, it was the generally thought that oral regimens should be prioritised to avoid the significant side effects of the injectable agents, paving the way for moves towards all-oral regimens (i.e. a move away from injectables).

STREAM Stage 2 started in April 2016 and involved the addition of two further treatment arms: regimen C or '9-month all-oral' and regimen D or '6-month' (see table 4 for drugs, dosages and route of administration).

Randomisation to regimen A was dropped early as shorter regimens were already in use.[25] Similarly, randomisation to regimen D was also stopped early because oral 6-month regimens were already being evaluated in phase-III trials.[25]

The final clinical analysis of STREAM Stage 2 was published in 2022[26]. 71% of participants on the 9-month injectable-containing regimen versus 83% of participants on the 9-month all-oral regimen achieved favourable outcomes. While the 9-month injectable-containing regimen was non-inferior to the 20-22 injectable-containing regimen in Stage 1, it was now inferior to the 9-month all-oral regimen tested in Stage 2. Of 134 participants allocated to the 6-month regimen (prior to it being terminated early), 91% had a favourable outcome, compared to 69% assigned to the concurrent control regimen. [26]

Evidence from STREAM Stage 1 and 2 represented an important contribution to the growing body of evidence available to support treatment guidelines for MDR/RR-TB. The 2020 WHO guidelines were based only on observational data[27], and STREAM validated the recommendation of a 9-month bedaquiline-based oral regimen. In addition, STREAM provides information on an effective 6-month alternative which could be a valid option in certain settings, where there are concerns about toxicity and side effects of some of the drugs included in the currently recommended regimen.

Table 3. Summary of regimens tested in STREAM

	Duration	**Injectable-containing**	**Bedaquiline-containing**	**Included in Stage 1**	**Included in Stage 2**
Regimen A	20-22months	x		x	x, but recruitment stopped early
Regimen B	9-months	x		x	x
Regimen C	9-months		x		x
Regimen D	6-months	x	x		x, but recruitment stopped early

Table 4. Drugs, dosages and route of administration of treatment regimens tested in STREAM

	Regimen A	*Regimen B*	*Regimen C*	*Regimen D*
Drugs, mode of administration and dosages for patients whose weight was higher than 50kg	Locally used regimen recommended by WHO in 2011	Moxifloxacin (800mg, oral) Clofazimine (100mg, oral) Ethambutol (1200mg, oral) Pyrazinamide (2000mg, oral) Kanamycin¯ (1g, intensive phase only, injectable) Isoniazid (600mg intensive phase only, oral) Prothionamide (750mg, intensive phase only, oral)	Levofloxacin (1000mg, oral) Clofazimine (100mg, oral) Ethambutol (1200mg, oral) Pyrazinamide (2000mg, oral) Bedaquiline˜ (400mg, oral) Isoniazid (600mg, intensive phase only, oral) Prothionamide (750mg, intensive phase only, oral)	Levofloxacin (1000mg, oral) Clofazimine (100mg, oral) Pyrazinamide (2000mg, oral) Bedaquiline˜ (400mg, oral) Kanamycin# (1g, intensive phase only, injectable) Isoniazid (600mg, intensive phase only, oral)

¯Kanamycin was administered in regimen B as an injectable daily for the first 12 weeks and then three times a week for the remainder of the intensive phase (four weeks)

˜400mg of Bedaquiline were administered daily for the first two weeks, then the dose and frequency were reduced to 200mg three times a week for the remainder of the treatment duration (38 weeks)

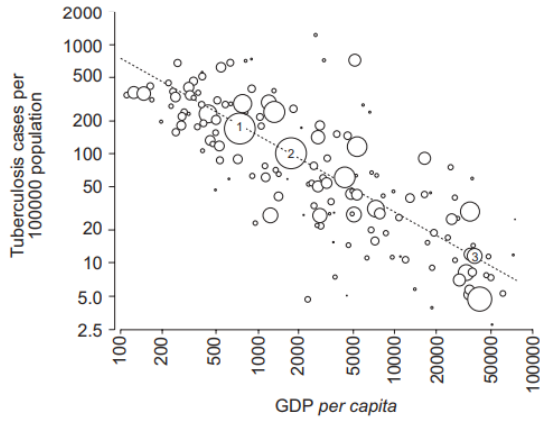
#Kanamycin was administered in regimen D as an injectable daily for the whole duration of intensive phase (eight weeks)

6. The economics of tuberculosis

Historically, TB has been a 'social disease', with the poorest people having the highest risk of infection.[28] Studies assessing the TB burden in specific vulnerable populations such as prisoners, the homeless or people from poor settings showed there is an association between social status and TB risk.[28] As TB is transmitted through infectious droplets, people living or working in settings where TB prevalence is high are at a higher risk of infection. These include crowded or poorly ventilated spaces more commonly inhabited by vulnerable populations. Moreover, TB is more easily transmitted to people with weaker immune systems, such as those living with HIV or malnourished (often due to food insecurity). These, cumulated with smoking, diabetes, harmful alcohol use and indoor air pollution (that have a higher prevalence in vulnerable populations) are important risk factors. Therefore, the higher risk of TB among those in the lower socioeconomic groups is a result of the greater exposure to some of the risk factors above. Importantly, people in this group are generally less likely to have full access to high quality health care.

There is also a clear correlation between countries per capita Gross Domestic Product (GDP) and TB incidence (i.e. the higher the GDP, the lower the TB incidence)[29] (figure 4).

Figure 4. Relationship per capita GDP and incidence of TB per 100,000 population



1-India, 2-China, 3-United Kingdom. Source: Janssens & Rieder[29]

The economic costs of TB can be substantial for both patients and society. A systematic review showed that the mean direct costs incurred by TB patients can vary from US$4 in Egypt to US$3525 in China, with mean costs being US$432 per episode for DS-TB patients and US$672 for MDR-TB patients[30]. These costs mainly consisted of non-TB drugs, food while inpatient and transport.

In addition to direct costs, patients also incur indirect costs due to their inability to work during part or whole treatment duration. Previous studies suggested that, on average, TB-affected patients lose three to four months of work time, which often results in a 20-30% of annual household income loss.[31] Premature death of the TB sufferer can also occur, leading to further long-term income losses, in addition to the possible debts and funeral costs left to the family. To cover these costs, households use different coping mechanisms, such as borrowing or selling assets, with a recent systematic review showing that 81% of MDR-TB patients incur catastrophic costs.[32]

Studies have repeatedly shown[33,34] that high patient treatment costs can delay treatment start or even deter patients from seeking care, leading to worse outcomes and more severe illness. A recent systematic review showed that This in turn, can increase the burden of TB. Furthermore, catastrophic costs can frequently push families into poverty and disrupting the households' long term economic stability.[35] Efforts aimed at reducing catastrophic costs have included improved access to affordable TB treatment and care and implementing social protection programmes to help provide a buffer to households from the economic shocks of TB.[36,37]

These high direct and indirect costs have consequences beyond treatment end and affect the households' disposable income long-term. Meghij et al[38] showed that TB also has a long-term effect on income and employment. In this study, income and employment were usually lowest at TB-treatment completion, with limited economic recovery in the first year after treatment: fewer people were in paid work (63% after TB treatment completion vs. 72.4% before TB treatment start), median incomes were lower (US$44.13 after TB treatment completion vs. US$72 before TB treatment start) and more patients were leaving in poverty compared to before TB disease (earning<US$1.90/day: 57.7% after TB treatment completion vs. 41.6% before TB treatment start). Moreover, half of participants (184/368) reported continuous use of the coping mechanisms.[38]

Beside costs, studies suggest that overall well-being and health-related quality of life are also affected in patients with TB. In a study conducted in the Philippines, both the number of symptoms and breathlessness as an individual symptom were strongly negatively associated with HRQoL in both physical and mental aspects.[39] Patients with active TB also generally perceive their health status to be worse as compared to people with latent TB or previously cured TB.[40] While some of the disease and treatment-related health consequences of TB will improve once treatment has ended[41], there also could be some long-term or life-long effects, with studies consistently reporting that quality of life of previous TB patients remained significantly worse than the general population[42].

Economic evaluations play a crucial role in the fight against TB by providing decision-makers with information on the cost and cost-effectiveness of alternative treatment regimens. However, the economic evidence on shorter MDR-TB treatment regimens and treatment delivery methods is sparse.

A recent systematic review of economic evaluations for active TB treatments showed that shorter regimens for both DS and MDR-TB are cost-effective when compared to longer regimens, as well as decentralised care that employed the use of home or mobile devices compared to hospital-based care in low and middle-income countries.[43] However, all studies except one were modelling studies (Markov or decision tree) and did not directly collect efficacy outcomes, patient-reported costs or quality-of-life data. The only observational study included in the review compared standard of care to a community-based model and showed that cost per successfully treated patient was 3 to 4.5 lower in the community-based model of delivering TB care.[44] While community DOT is available as an alternative to health-facility DOT, patients would still be required to travel daily leading to reduced treatment completion rates because of the costs, inconvenience and stigma. There is some evidence[45–47] that the use of electronic, mobile phone applications, known as digital interventions or the use of patient-centred strategies can reduce DS-TB patient costs while achieving similar treatment completion rates as in-person DOT. However, such evidence for the shorter MDR-TB regimen is missing and a clear understanding of how programmatic changes in treatment delivery would affect patients and health systems is needed.

Due to a lack of directly measured economic (costs and quality of life) data, WHO guidelines have also relied on modelling work to influence policy, with theirs and other modelling studies showing that shorter and oral regimens have the potential to reduce health system and patient costs, however, the timing and magnitude of the reductions was uncertain. The overall certainty of evidence was ‘very low’. This work showed that a 9-month all-oral regimen would provide cost savings relative to the 9-month injectable-containing regimen, by reducing the costs associated with the management of adverse events resulting from the injectable agent (nephrotoxicity and ototoxicity). Moreover, expenses related to audiometry tests and regular assessments of renal toxicity would also contribute to the cost savings for the all-oral regimen, relative to the injectable-containing regimen.[27] However, these modelling findings needed to be tested in a formal economic evaluation as they lacked directly measured economic data comparing the regimens.

Recent studies estimated that, under current decrease in tuberculosis deaths of 2% per year, there will be 31.8 million TB-related deaths from 2020 to 2050. This corresponds to an economic loss of $US17.5 trillion.[48] The aggregate economic losses are highest in the south Asia, east Asia and Pacific regions with

mean life expectancy losses per person highest in sub-Saharan Africa. Welfare losses due to TB would burden sub-Saharan Africa, although the effects are less apparent due to lower per-capita incomes.

Therefore, there is a clear need for robust economic evidence of the short and oral MDR-TB regimens as well as for the alternative treatment delivery strategies, as there is evidence (derived from DS-TB for the use of digital technologies and patient-centred care for treatment delivery and from the modelling work for MDR-TB) that these can reduce both health system and patient costs and improve treatment adherence and outcomes, reducing the disease burden. Tackling the TB epidemic requires a multi-faceted approach, including both clinical and economic evidence to ensure that patients start treatment timely and continue until completion.[49] Considering the scale of the issue and the limitations in budgets, it is imperative that funds are spent wisely based on timely and reliable research.

In the next sections I will discuss the thesis objectives, present the work conducted and discuss its contribution in tackling TB.

Thesis Objectives

Against this background of rapidly evolving MDR-TB treatment options and guidance, and the global policy objectives of providing patient-centred care, and in the context of scarce health care resources, the specific objectives of the work presented in this thesis were:

1. To provide robust and timely economic evidence to inform MDR-TB treatment guideline recommendations
2. To evaluate alternative models of MDR-TB treatment delivery with a focus on identifying the optimal approach from a patient and health system cost perspective

How the papers achieve the thesis objectives

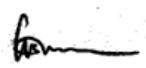
To provide robust and timely economic evidence to inform MDR-TB treatment guideline recommendations we conducted two within trial economic evaluations (paper 1 and paper 3), with the latter supported by a peer reviewed published protocol (paper 2), guarding against selective reporting. As mentioned in Section 5.1, STREAM Stage 1 compared a novel, short, 9-month injectable-containing regimen for MDR-TB to the 20-22-month SOC at the time and was anticipated to reduce patient and health system treatment costs. STREAM Stage 2 compared the 9-month injectable-containing regimen tested in Stage 1 with a novel all-oral 9-month regimen and separately with a shorter 6-month injectable-containing regimen. The all-oral 9-month regimen and the 6-month injectable-containing regimen both contained a novel drug, bedaquiline, being tested in a Phase-III trial for the first time. These trials were conducted with the primary purpose of evaluating these novel treatment regimens and provided a unique opportunity to supplement clinical evidence with robust economic evidence to guide uptake and implementation of regimens by national TB programmes. Furthermore, they provided the opportunity to give evidence on the economic impact of MDR-TB, contributing to the global policy goals of financial protection and elimination of catastrophic costs for patients.

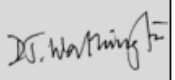
Outside of the trial setting, health systems aim to deliver MDR-TB treatment regimens in a patient-centred manner in accordance with WHO guidance on treatment support[50]. Additionally, given the pervasive problem of high patient costs and high incidence of catastrophic costs, there is a need to

evaluate the potential impact of alternative MDR-TB treatment care models on patient costs. The economic evidence is important both to inform health system choices about which strategies to implement and support planning and financing and to identify the extent to which alternative approaches affect patient costs. Phase-IV evaluations would be the best suited approach to address these questions, however before investing in these, and to move closer towards prioritising which strategies to roll out for further evaluation, we decided to take a modelling approach, that enabled us to use the rich data from the Phase-III STREAM trial, to help identify optimal approaches for implementation. We conducted a modelling study to examine health system and patient costs for delivering MDR-TB DOT using patient-centred approaches versus SOC facility-based delivery (paper 4). A second study explored and compared, for the first time, a range of promising new digital health technologies and family-observed DOT to be used for the short MDR-TB treatment regimens (paper 5). There was emerging evidence that digital and patient-centred DOT delivery methods can improve adherence and reduce costs in DS-TB, however there was no economic analysis for the novel shorter MDR-TB regimen.

Summary of studies

To achieve the aim and objectives of this PhD, the work has been conducted between 2018 and 2022, with publication dates ranging from 2020 to 2023. Laura Rosu is submitting the following papers for consideration as part of a PhD by published work in Global Health at the Liverpool School of Tropical Medicine.

Objective	Study number	Title	Journal and Year	Author List	Candidate contribution	Senior author/joint co-author signature
1	1	Economic evaluation of short treatment for multidrug-resistant tuberculosis, Ethiopia and South Africa: the STREAM trial Doi: http://dx.doi.org/10.2471/BLT.19.243584	WHO Bulletin, 2020	Jason J Madan, **Laura Rosu**, Mamo Girma Tefera, Craig van Rensburg, Denise Evans, Ivor Langley, Ewan M Tomeny, Andrew Nunn, Patrick PJ Phillips, I D Rusen & S Bertel Squire for the STREAM study health economic evaluation collaborators (N.B. JJM and LR contributed equally in the writing of this study)	LR conducted the analysis and with JM, contributed to the interpretation and write up of the results.	S Bertel Squire:  Date: 28.02.2023 Jason J Madan:  Date: 02/03/2023
1	2	Economic evaluation protocol of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial Doi: 10.1136/bmjopen-2020-042390	BMJ Open, 2020	**Laura Rosu**, Jason Madan, Eve Worrall, Ewan Tomeny, S Bertel Squire, on behalf of STREAM Study Health Economic Evaluation Collaborators	LR contributed to the design of the study and drafted the first version of the analysis protocol	S Bertel Squire:  Date: 28.02.2023
1	3	Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial Doi: https://doi.org/10.1016/S2214-109X(22)00498-3	The Lancet Global Health, 2022	**Laura Rosu**; Jason J Madan; Ewan M Tomeny; Malaisamy Muniyandi; Jasper Nidoi; Mamo Girma; Valentina Vilc; Priyanka Bindroo; Rajdeep Dhandhukiya; Adamu K Bayissa; Daniel M. Kokebu; Narendran Gopalan; Rajesh Solanki; Anuj K Bhatnagar; Elena Tudor; Bruce Kirenga; Sarah K Meredith; Andrew Nunn; Gay Bronson; I.D. Rusen; S Bertel Squire; Eve Worrall for the STREAM study health economic evaluation collaborators (N.B. SBS and EW are joint senior authors)	LR made a substantial contribution to the conception and design, organisation, and conduct of the study. She supervised data collection in all countries, contributed to data collection, and carried out data cleaning, analysis, and interpretation. She designed the figures and tables, produced the first draft of the manuscript, and incorporated critical feedback and revisions from co-authors	S Bertel Squire:  Date: 28.02.2023 Eve Worrall:  Date: 24.02.2023

2	4	Cost of treatment support for multidrug-resistant TB using patient-centred approaches: a model- based method Doi: https://doi.org/10.1186/s40249-023-01116-w	Infectious diseases of poverty, 2023	**Laura Rosu**, Lucy Morgan, Ewan M Tomeny, Claire Worthington, Mengdi Jin, Jasper Nidoi, David Worthington	LR made substantial contributions to the conception of the work, acquisition of the data, analysis and interpretation of data and contributed to the drafting of the work and revised it critically for important intellectual content.	David Worthington:  Date: 28.02.2023
2	5	Cost of digital technologies and family- observed DOT for a shorter MDR-TB regimen: a modelling study in Ethiopia, India and Uganda	Submitted: BMC Health Services Research, 2023	**Laura Rosu**, Jason Madan, Gay Bronson, Jasper Nidoi, Mamo Girma, Muniyandi Malaisamy, Bertie S Squire, Eve Worrall on behalf of the STREAM collaborators	LR made a substantial contribution to the conception and design and conduct of the study. She carried our data analysis and interpretation. She designed the figures and tables, produced the first draft of the manuscript and incorporated critical feedback and revision form co-authors	Eve Worrall:  Date: 24.02.2023

Paper 1. Economic evaluation of short treatment for multidrug-resistant tuberculosis, Ethiopia and South Africa: the STREAM trial

Primary objectives: To assess the cost and cost-effectiveness of a 9-month injectable-containing regimen (short) in comparison with the 2011 WHO recommended regimen of 20-22 months duration (long) and investigate the nature, magnitude and timing of the changes in costs for participants and health systems as a result of switching to the short MDR-TB regimen.

Methods: Data were collected at two sites in Ethiopia and two in South Africa, by the health economic focal persons in each country. All patients were followed up for 132 weeks from baseline (week 0). Pathways representing typical activities of care were constructed at each site following discussions with the stakeholders in each country. The resources involved in delivering these activities were identified from time and motion studies, supplemented by interviews with relevant clinical and managerial staff and costed using local unit costs in each country. Cost data related to inpatient stay, serious adverse event (SAE) management, monitoring tests, staffing, consumables and social support were collected in each country. Accurate records and admission and discharge dates were not available, so time to sputum smear conversion was used as a proxy to inpatient stay duration. Health system costs were calculated for each participant from baseline until treatment completion (week 40 for the short regimen and week 82 for the long regimen).

Data on participant costs and socioeconomic status were collected at scheduled assessment visits using an adapted STOP-TB questionnaire (appendix I). The questionnaires were administered every 12 weeks from randomisation until week 132.

A cost-effectiveness analysis was conducted by calculating the incremental cost per unfavourable outcome avoided.

Boostrapping was used to test parameter uncertainty. We simulated 1000 estimates of mean costs and outcomes, which were used to construct 1000 simulated cost-effectiveness ratios. The results of this are presented as cost-effectiveness acceptability curves, which show the proportion of simulation results in which the short regimen was cost-effective, using a range of willingness-to-pay thresholds.

Results: Despite the additional cost of electrocardiogram (ECG) monitoring required for participants on the shorter regimen, reductions in social support, laboratory tests and medication (Ethiopia) and medication and staff (South Africa) costing categories made the short regimen cheaper by 25% in Ethiopia and 21% in South Africa, when compared to the long regimen.

Inpatient costs were the largest category of expenditure for both regimens in both countries, even when the unit cost was varied in a sensitivity analysis. This is due to the long and similar inpatient stay durations (9.63 weeks in Ethiopia on average and 9.22 weeks in South Africa) for both regimens.

The bootstrap analysis on health system costs showed that the short regimen is highly likely to be cost-effective (probability greater than 95%) if the value decision-makers place on avoiding an unfavourbale outcome was less than $19,000 in Ethiopia and US$14,500 in South Africa (figure 5).

In total, participants in the short regimen in Ethiopia spent less by US$238.0 than participants in the long regimen over treatment course, of which 95% related to reduced spending on supplementary food (e.g. meat, fruit and energy drinks) bought to complement their MDR-TB treatment. The savings for attending

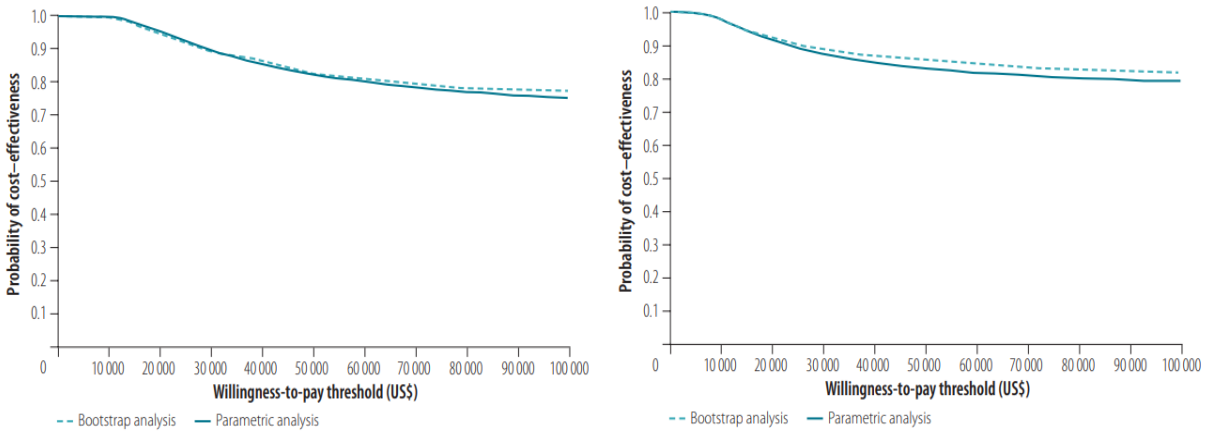
monitoring visits were US$64.0 in South Africa. Due to insufficient data, we could not estimate supplementary food expenditure spend in South Africa.

Participants were mostly unwilling or unable to estimate their typical monthly income, however, participants in Ethiopia were able to report the number of hours they worked before and throughout treatment and we used this as a proxy to measure indirect costs (Figure 6). Overall, the mean additional time worked per participant on the short regimen during the 132 weeks of treatment and follow-up was 667 hours (95% CI: 193 to 1127). Using published income estimates, this increase in productivity corresponds to a saving in indirect costs of US$175.7 per participant. There were insufficient data to make similar estimates for South Africa.

The 9-month injectable-containing regimen led to substantial savings for both health system and participants compared to the control. We showed that the additional safety monitoring for the short regimen was greatly outweighed by other savings. There were also some important, unexpected findings, on the timing and drivers of these savings.

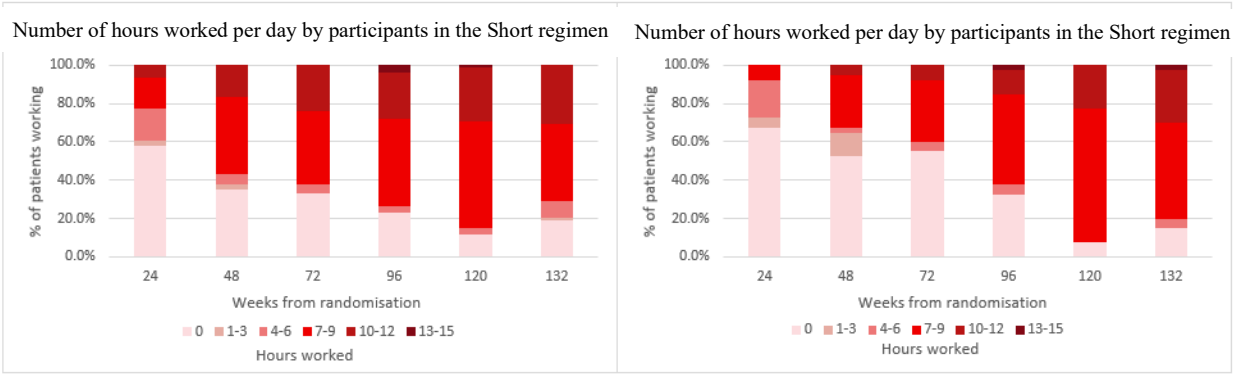
These and the final published clinical results contributed to the 2019 WHO consolidated guidelines[51] endorsing shortened regimens with economic benefits for both patients and health systems.

Figure 5. Probability that the short MDR-TB treatment was more cost-effective than the long treatment, by willingness to pay to avoid unfavourbale outcomes, from a health system perspective. Left Ethiopia, right South Africa.



Source: Rosu et al, WHO bulletin [52]

Figure 6. Participant-reported number of hours worked per day in Ethiopia for both control and study regimens



Source: Rosu et al, WHO Bulletin, supplement[53]

Paper 2. Economic evaluation protocol of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial

Primary objective: To adhere to best practice research integrity by proposing the economic evaluation methodology *a priori* in order to obtain peer review of those methods, and to sensitise the global community to the nature of the upcoming findings, especially given their policy relevance

Methods: The protocol paper set out the objectives of the economic evaluation:

1) Primary: to estimate the cost-utility of the two MDR-TB treatments: a 9-month all-oral regimen (Oral) and a 6-month injectable-containing regimen (6-month) versus a 9-month injectable-containing regimen (Control)
2) Secondary: to evaluate the cost-effectiveness of the regimens using trial's efficacy outcomes.

We proposed methods to collect health system and participant cost data, as well as measuring participants' quality-of-life using EQ-5D-5L from baseline until week 76 of treatment and follow-up and presented plans to use QALYs as the outcome in the cost-utility analysis and the pooled STREAM primary endpoint of favourable outcome at week 76 in the cost-effectiveness analysis.

We proposed a mix of top-down and bottom-up approaches to calculate the health system costs. As in STREAM Stage 1, a full assessment of health system costs of delivering the MDR-TB regimens, including tests performed, consumables used, inpatient stay costs, drugs administered, management of SAEs was planned.

As in STREAM stage 1, we proposed to collect patient data every 12 weeks during the patient assessment visits for the clinical trial. We specified plans to calculate total direct cost per participant receiving MDR-TB treatment including costs for attending DOT, scheduled and unscheduled visits, as well as costs related to supplementary food expenditure, and to include costs for patients and their guardians. We planned multiple imputation techniques to address the missing data and several planned sensitivity analyses alongside bootstrapping to explore sampling uncertainty.

A key lesson from STREAM stage 1 was that cost surveys were sometimes not fully completed due to the participants needing to leave the facility to catch public transport. Hence, we decided not to add any additional questions to STREAM2, to avoid increasing the already high burden faced by participants for responding to the health economic questionnaire. For this reason, no additional questions were added to estimate household income.

Moreover, in Stage 1 it was difficult to assess cost-effectiveness as no threshold values were available for avoiding an unfavourable outcome, hence the addition of the QALY as an outcome of the analysis was considered important. Thus, the EQ-5D-5L questionnaire was added and used to collect participant-reported quality-of-life data in Stage 2. Anticipating a lack of tariffs for some STREAM countries, the protocol set out plans to convert the EQ-5D-5L into health utility scores using the most appropriate tariff for each country (based on geographical proximity and economic context and proposed Indonesia for India, Ethiopia for Ethiopia and Uganda and Poland for Moldova.

The protocol has been reviewed extensively by the co-authors and the study funder as well as undergoing peer review.

Paper 3. Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial

Primary objective: To assess the cost-utility of a short, 9-month all-oral regimen (oral) in comparison with a short, 9-month injectable-containing regimen (control) tested in STREAM Stage 1. Secondary objectives included the assessment of the cost-utility of a 6-month injectable containing regimen (6-month) versus control.

Methods: Analyses covered the period from randomisation until week 76, a post-treatment follow-up of 36 weeks for the Oral and Control regimens and 48 weeks for the 6-month regimen.

Participant direct cost data and health system cost data were collected and analysed per protocol (see appendix 3 for participant questionnaires used). Indirect costs were estimated using the output approach, by subtracting the self-reported individual income during tuberculosis treatment from the participants' self-reported pre-tuberculosis income, pro-rata, for the 76 weeks of follow-up.

Missing values in participants' responses for participant (and guardian) costs incurred for attending directly observed treatment and assessment visits (transport and food), lost income, and supplementary food expenditure were imputed using chained imputation models using a predictive mean matching algorithm.[54]

Although not initially planned for in our protocol, we also calculated catastrophic costs. However, we considered total participant costs to be catastrophic if they exceeded 20% of annual individual income, approximating to the WHO definition[55] that uses household income. This was done for several pragmatic reasons: from Stage 1 we learned that income is a sensitive topic and wanted to avoid compromising the indirect cost calculations, also collecting total household income would have required us to add additional questions in and this was not feasible. It would also have required us to obtain consent from all household members which was also considered unfeasible, or to ask trial participants to disclose income of other household members which would have potentially been difficult and risked inaccuracy.

Inpatient 'hotel' costs (which include the cost of an overnight stay, basic supplies and meals) were calculated by dividing the total annual expenditure on hotel costs by the number of annual inpatient stay days, for each institution. Public hospital records were used where possible, supplemented with data from private hospitals or market prices. As in Stage 1, treatment logs were used to calculate medication intake for each participant, which were then multiplied by the Global Drug Facility (GDF) unit costs to estimate regimen medication costs. In Stage 2 we also included salvage regimen costs in the health system costs.

Cost-effectiveness acceptability curves were created to address decision uncertainty. The threshold values included ranged from US$0 to US$20,000. The regimens were considered to have a high probability of being cost-effective if this exceeds more than 80%. Cost-utility and cost-effectiveness analyses were conducted from the provider perspective and then from the societal perspective, by adding total participant costs to the provider costs.

To aid interpretation, ICERs in the cost-utility analysis were compared with the upper bound of published purchasing power parity adjusted cost per QALY-gained thresholds of $696 in Ethiopia, $2781

in India, $2400 in Moldova, and $725 in Uganda.[56] There were no threshold values available to interpret the results of the cost-effectiveness analysis in a similar way.

Results: Total participant costs were lower in the oral regimen than control in Moldova and Uganda, and higher in the oral regimen group than the control group in Ethiopia and India. Within direct costs, supplementary food was the main cost driver, as in Stage 1, with participants in the control regimen group spending more on supplements than those in the oral regimen group in Ethiopia, India and Moldova, with the opposite finding in Uganda.

The proportion of participants facing catastrophic costs within the trial was 81% or more in all regimen groups and countries.

Total provider cost was higher in the oral regimen group than the control group in all countries. There were some provider cost savings in outpatient visit and staff cost categories, but these did not offset the higher regimen medication costs in the oral regimen group. Moreover, in terms of monitoring tests, the major cost drivers were laboratory tests required for monitoring both oral and injectable-containing regimens; the injectable-regimen-specific monitoring tests were not a major cost driver.

The oral regimen was associated, on average, with more QALYs over the 76 weeks of follow-up in Moldova, fewer in India and Uganda, and similar in Ethiopia. Across all trial sites, a pooled favourable outcome was achieved by 83% of participants in the oral regimen and 71% of participants in the control regimen.

From a provider perspective, the oral regimen resulted in higher provider costs and the same or lower QALYs in Ethiopia, India and Uganda, so was dominated by the control regimen and not likely to be cost-effective. In Moldova, the oral regimen resulted in higher costs but also higher QALYs, however the incremental cost-effectiveness ratio (ICER) was higher than the upper bound of the published Moldovan WTP threshold, and so not likely to be cost-effective either. From a societal perspective the conclusions remain unchanged for Ethiopia, India and Uganda. However, the societal costs are lower in Moldova in the oral regimen compared to control, making the oral regimen dominant and cost-effective compared to the control from the societal perspective.

From the provider-perspective cost-effectiveness analysis, the oral regimen had a high (>80%) probability of being cost-effective compared with the control regimen if the WTP thresholds for each additional favourable outcome are more than $4500 in Ethiopia, more than $1900 in India, more than $3950 in Moldova, and more than $7900 in Uganda. From a societal perspective, the WTP thresholds must exceed $15 900 in Ethiopia, $3150 in India, and $4350 in Uganda for the oral regimen to have a high probability of being cost-effective. In Moldova, the oral regimen results in lower costs and additional favourable outcomes versus the control regimen, so it is dominant and cost-effective (figure 7).

Eight participants in Moldova and nine participants in Uganda were assigned to the 6-month regimen, so the analysis of the 6-month regimen was not conducted in these two countries.

Total provider costs and participant costs were lower in the 6-month regimen group than the control group in both Ethiopia and India and it also resulted in similar QALYs in Ethiopia and more QALYs in India.

Comparing all three regimens from a provider perspective, in Ethiopia and India, resulted in the Oral regimen being dominated by the 6-month regimen in the cost-utility analysis and was thus eliminated from the comparison. The analysis was then reduced to the Control vs. Six-month comparison presented below.

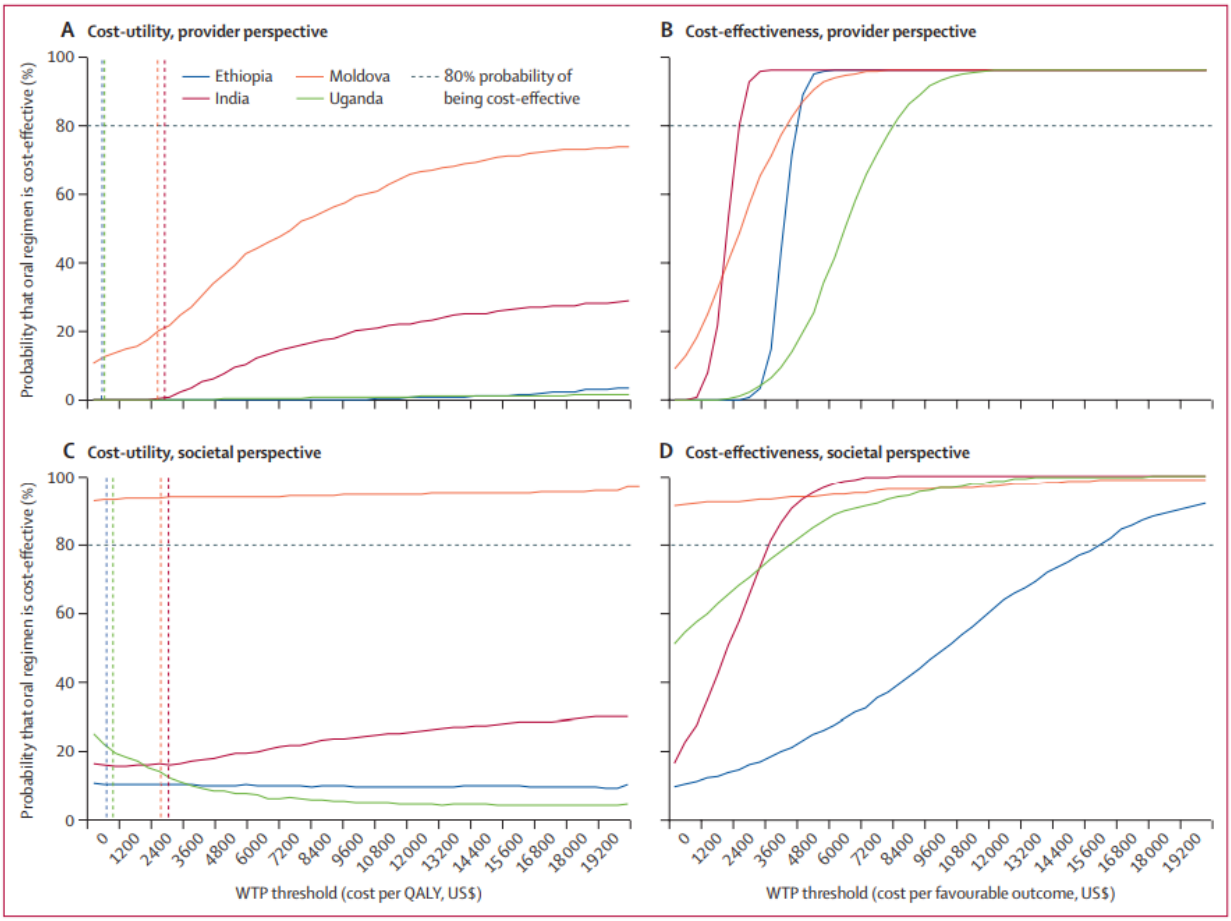
In Ethiopia, the 6-month regimen had lower provider and societal costs and similar QALYs versus the control regimen. There is a high probability that the 6-month regimen is cost-effective against published Ethiopian threshold estimates of $686 per QALY. In India, the 6-month regimen also resulted in lower provider and societal costs, and higher QALYs, making it dominant and highly likely to be cost-effective. The 6-month regimen had more favourable outcomes (by 20%) than the control regimen making the 6-month regimen dominant and cost-effective from both perspectives.

Results were sensitive to the cost of bedaquiline. A reduction in the price per 100 mg pill from $1.81 to $1.00 would make the oral regimen cost-effective in India (ICER $1018 < WTP threshold $2781) and Moldova (ICER $517 < WTP threshold $2400) from a provider-perspective cost-utility analysis. Making the same change to bedaquiline pricing, the cost-effectiveness analysis shows that the oral regimen would dominate the control regimen in India from a provider perspective and have a high probability of being cost-effective from a societal perspective. The oral regimen would also have a high probability of being cost-effective in Moldova from the provider perspective (and become more attractive). The 6-month regimen would be even more attractive in relation to the WTP thresholds.

Results were robust to using the country-specific efficacy outcome (instead of the pooled estimates), complete-case analysis (instead of multiple imputation), excluding the retrospectively collected data in India and Uganda or an increase of up to US$150 per participant to treat adverse events.

Our findings provide robust evidence on the cost-utility and cost-effectiveness of two new MDR-TB regimens. The data on likely costs, potential savings and patient-reported outcomes can be used to guide update and implementation of regimens by national tuberculosis programmes.

Figure 7. Cost-effectiveness acceptability curves from the economic evaluation of the oral regimen versus control regimen



Source: Rosu et al, Lancet Global Health[57]

Paper 4. Cost of treatment support strategies for multidrug-resistant TB using patient-centred approaches- a model-based method

Objective: To evaluate the health system and patient costs associated with the adoption of patient-centred strategies for delivering directly-observed therapy for MDR-TB

Methods: This study evaluates two alternative management strategies for MDR-TB in Ethiopia: a patient-centred and a hybrid model, which are each then compared to the SOC which require patients to travel daily to a health-facility for DOT. The patient-centred strategy sees patients treated as outpatients throughout their treatment, hospitalised only if they experience a serious adverse event (SAE). The nurse delivers medication during these visits (eliminating patient travel to health centres) and once a month collects a sputum sample for testing. The Hybrid strategy sees patients travelling to collect drugs and receive injectable treatment during the intensive phase only, and then follows the patient-centred approach during continuation phase. For both alternative management strategies we considered daily DOT visits, testing more less frequent (weekly) visits in a scenario analysis.

The study consists of two components: a discrete event simulation (DES) operational model which generates the treatment pathways of 1000 hypothetical patients under each of the three treatment delivery strategies of interest; and a cost model that applies unit costs according to how long patients spend in the different parts of their treatment pathways as determined by the DES model. The DES model was built to incorporate the three strategies, with pathways reflecting patient journeys throughout treatment (figure 8).

STREAM prices were used in calculating total health system and patient costs. Total staff costs were calculated by multiplying the mean travel and visit time in minutes by the nurse cost per minute as calculated in STREAM, to which we added the return transport cost. Total patient transport costs were calculated for each strategy by multiplying the mean cost of a single health facility visit by the number of visits made. We also included the weekly costs associated with the supplementary food expenditure; this was multiplied by the number of weeks in treatment a patient was not hospitalised.

Results

The patient-centred and hybrid strategies are less costly than SOC, from both a health system and patient perspective (Table 5).

The patient costs are lower in the hybrid and patient-centred strategies because patients are travelling less or not at all for treatment-related purposes. Guardian accompaniment caused some increase in patient costs, from 4% for the patient-centred strategy to 27% for the SOC. Total costs of a patient with a guardian in the SOC represent 47% of an estimated annual income of $1248.

The results were robust to the sensitivity analyses and scenarios tested.

Figure 8. The pathway model for the base-case strategy

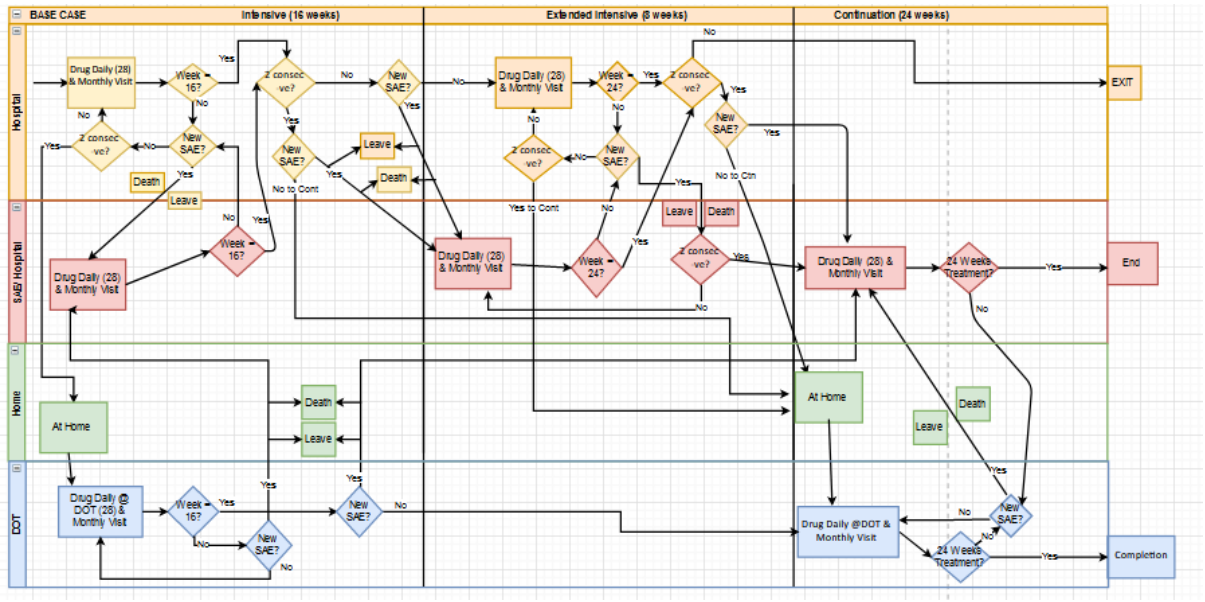


Table 5. Mean per-patient health system and patient costs for the three strategies (US$)

	SOC	Patient-centred (daily DOT)	Hybrid (daily DOT)	Patient-centred (weekly DOT)	Hybrid (weekly DOT)
Health System	3037	2818	2761	2697	2693
Patient	463	74	311	74	311
Patient with guardian	589	77	368	77	368
Societal, including guardian	**3626**	**2895**	**3129**	**2774**	**3061**

Paper 5. Cost of digital technologies and family-observed DOT for a shorter MDR-TB regimen: a modelling study in Ethiopia, India and Uganda

Objective: To evaluate the health system and patient costs associated with the adoption of digital technologies or family observed directly-observed therapy for MDR-TB

Methods: In this study we used a decision analytic model to evaluate VOT, 99DOTs and family-observed DOT compared to SOC DOT. VOT is a smartphone-based approach that allows for remote treatment monitoring through either live or patient-recorded videos. 99DOTS employs a low-cost mobile phone-based technology- when dispensing pills hidden phone numbers are revealed that the patient needs to call at. Under family-observed DOT daily treatment is supervised by a household member selected by the patient

In Ethiopia, India and Uganda treatment is delivered using SOC DOT, meaning that MDR-TB patients travel daily in Ethiopia and Uganda and three times a week in India, to district health centres where they receive and take their TB medication.

The decision analytic model was developed based on the SOC DOT model in each country. It was then populated with probabilities calculated based on the STREAM Stage 2 data and costs from the same source for the 9-month, all-oral MDR-TB regimen (figure 9).

It was assumed that all DOT approaches yield the same cure, failure, LTFU and death rates. We made this conservative assumption as there is no randomised trial evidence regarding the impact of using alternatives to in-person DOT on treatment outcomes for shorter MDR-TB regimens. Moreover, we assumed that SAE result in a treatment extension of 8 weeks.

Total number of DOT visits for each strategy was 280 in Ethiopia and Uganda, and 120 in India. In accordance with the 2022 operational handbook on tuberculosis[50], we assumed that patients were travelling monthly to the health facility for treatment and safety monitoring in addition to the DOT visits.

The main cost data source is the STREAM Stage 2 trial data, supplemented by market prices or published estimates for costing the digital DOT strategies.

In calculating the health system costs for VOT, we used market prices in each country for costing the smartphones and mobile data required. Smartphone penetration rates were also used to calculate the percentage of population requiring a device and mobile data.

For costing 99DOTS, we included the fixed costs as revealed by the manufacturer: costs for renting a toll-free line, the envelopes costs, SMS, call and staff packaging costs.

For family-observed DOT costs, it was assumed that the family-member did not receive any pay for supervising their relative's treatment. It was also assumed the family member was trained at the beginning of treatment and then every 12 weeks on how to monitor treatment adherence.

Staff costs performing the monitoring activities were added to each strategy.

Both direct and indirect patient costs from STREAM were used.

Probabilistic sensitivity analysis was conducted to assess parameter uncertainty, using 1000 Monte Carlo simulations. Also, lower lost to follow-up rates and higher relapse rates, thought to be consequences of the alternative DOT approaches were tested in the sensitivity analysis.

Results: When compared to SOC DOT, adoption of VOT or 99DOTS reduces patient costs by 97% in Ethiopia and Uganda, and by 93% in India (table 6).

Although family-observed DOT is slightly more expensive than VOT and 99DOTS in all countries due to the monitoring training required, it would still save patients over 90% of costs in all countries when compared to SOC.

From a societal perspective, SOC is the costliest approach in all three countries (table 6). This is closely followed by the VOT approach, with savings ranging from 4% in India to 10% in Ethiopia.

Family-observed DOT yields the highest savings from a societal perspective in Uganda, while 99DOTS is the cheapest strategy in Ethiopia and India.

Decreasing the LTFU by 5% and 10% made the alternative DOT approaches more attractive than in the base case as the societal costs slightly decreased. Results remained robust to an increased relapse rate of 6.5% though alternative DOT approaches costs have increased. They also remained robust when parameter uncertainty was tested in a probabilistic sensitivity analysis.

Figure 9. Visual representation of decision analytic model of standard of care and alternative DOT approaches

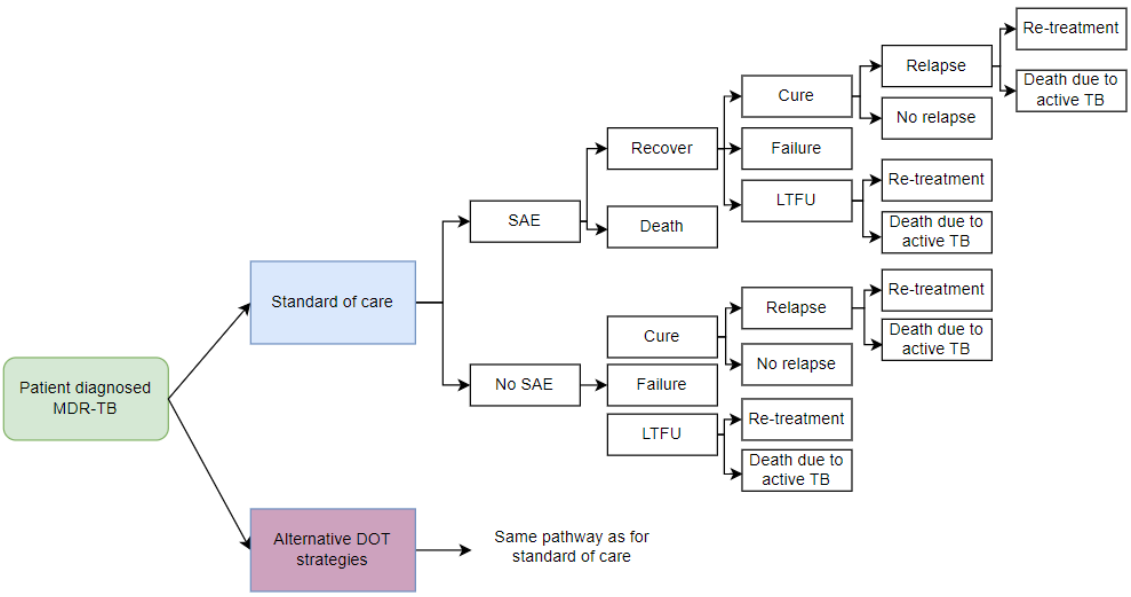


Table 6. Health system, patient and societal costs for each DOT strategy in each country (US$)

	Ethiopia (US$)			India (US$)			Uganda (US$)		
	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3790.4	572.3	4362.6	2003.3	324.2	2327.4	6348.6	888.6	7237.1
VOT	3999.9	17.9	4017.8	2201.7	22.7	2224.4	6716.7	27.7	6744.5
99DOTS	3769.3	17.9	3787.2	1980.4	22.1	2002.5	6151.2	27.4	6178.7
Family-observed	3765.4	26.3	3791.7	2005.0	31.8	2036.7	5975.0	29.5	6004.4

Thesis Discussion

1. Papers contribution to the thesis objectives

The first objective of this thesis was to provide robust and timely economic evidence to inform MDR-TB treatment guideline recommendations by conducting within trial economic evaluations of novel MDR-TB treatment regimens. This was addressed by presenting the economic impact on health systems of multiple MDR-TB regimens through the two phases of the STREAM trial.

In paper 1 it was presented the nature, magnitude and timing of the changes in costs from switching to the short, 9-month injectable-containing MDR-TB regimen. Although some reductions in health system costs were expected (due to reduced number of assessment visits, DOT visits and their associated costs), results showed that these were greater than the additional costs of cardiac safety monitoring required for the 9-month regimen, meaning that the 9-month regimen was cheaper from a health system perspective. Also, participants following the 9-month regimen spent less than those on the long, 20-22-months regimen in both countries, with most savings in Ethiopia coming from reduced spending on supplementary food, making the short regimen less expensive from a patient perspective too. The findings strongly support the adoption by policymakers of the short regimen for MDR-TB treatment in most, if not all, low-middle income settings. These and the final published clinical results contributed to the 2019 WHO consolidated guidelines[51] endorsing shortened regimens with economic benefits for both patients and health systems.

Paper 2 and paper 3 built on the findings of paper 1 and compared a 9-month, all-oral regimen with the 9-month injectable-containing regimen tested in Stage 1 (which acted as the control in Stage 2). I showed that total health system costs were higher in the 9-month all-oral regimen in all countries. Total participant costs were higher in two countries and lower in the other two, so there was no consistent pattern. I also showed that the oral regimen is unlikely to be cost-saving or cost-effective compared with the injectable-containing regimen of same duration. Although the oral regimen had superior clinical efficacy, the participant reported QALYs were not significantly different across the two intervention groups. In the health system perspective cost-utility analysis the ICERs exceeded realistic WTP per additional QALY thresholds in all countries. These findings were upheld in the societal-perspective analysis, except in Moldova, where the oral regimen was cost-effective. The trial endpoint (favourable outcome) was difficult to interpret because of the absence of any revealed WTP data, and difficult to meaningfully compare with other outcomes. However, it seems unlikely that in-country TB programmes would be willing to pay the amounts estimated by the bootstrap analysis (i.e., for the oral regimen to have a probability ≥80% of being cost-effective), which ranged from $1900 to $7900 per additional favourable outcome. Bedaquiline costs were an important cost driver for the 9-month all-oral regimen and sensitivity analyses showed that halving its price would make the regimen cost-effective in India and Moldova in the health system perspective cost-utility and cost-effectiveness analyses. The data on likely costs, potential savings and patient-reported outcomes can be used to guide uptake and implementation of regimens by national tuberculosis programmes. To enable cost-effective delivery of the 9-month all-oral regimen providers will need to allocate additional resources to treat MDR-TB.

The second thesis objective was to evaluate alternative models of MDR-TB treatment delivery with a focus on identifying the optimal approach from a patient and health system cost perspective. During the STREAM trial, across all sites, DOT took place at the healthcare facility and the percentage of patients experiencing catastrophic costs was high, regardless of the allocated regimen. Therefore, in paper 4 and

5, my aim was to identify how MDR-TB treatment delivery can be optimised and how much this will cost from both a health system and patient perspective to inform country level strategy decision and potential phase-IV evaluations (operational studies). This was achieved (in paper 4) through the development of patient-centred and hybrid pathway models to evaluate potential alternative care models in accordance with the End TB objectives for patient-centred care, and through a decision analytic model where I explored the costs of some of the most used approaches that could replace in-person DOT (paper 5).

In paper 4 an operational model of different MDR-TB treatment delivery strategies in Ethiopia was built based on the patient pathway I collected in STREAM. Using STREAM cost data, I then contributed to the calculation of costs of the three alternative strategies for delivering TB treatment: a strategy reflecting the SOC in Ethiopia, a patient-centred approach and a hybrid approach. Results showed that patient costs can be reduced under a hybrid or patient-centred approach, with a reduced contact time from seven days a week to one day a week. Apart from reducing the costs, these strategies have the potential to increase access to MDR-TB services, contributing to TB elimination. This study adds on the growing evidence that a decentralised, ambulatory care model in Ethiopia contributes to an increase in number of people tested and put on MDR-TB treatment[58]. The DES model itself is attractive as its flexibility means that it can be adapted to a range of setting to explore a range of strategies prior to scale up or evaluation.

Paper 5 presents the potential cost of implementing digital DOT or family-observed DOT for the delivery of MDR-TB treatment, using a decision tree model I built. The results indicate that use of VOT, 99DOTS and family-observed DOT as part of a 9-month all-oral MDR-TB treatment regimen could substantially reduce patient and societal costs in all countries. This could help protect TB-affected populations from catastrophic expenditure. Moreover, the alternative DOT approaches evaluated in this study permit DOT to take place according to the patients' circumstances, without requiring them to interrupt their usual activities.

With this thesis, I demonstrate how health system and patient costs vary by MDR-TB treatment regimen and by treatment delivery method. It illuminates the current patient experiences during treatment and how these can be optimised, to achieve the aims of reducing patient costs and avoid catastrophic costs.

2. Methods and lessons learnt

The addition of economic evaluations to randomised controlled trials give policy makers robust evidence on the cost and cost-effectiveness of the interventions tested. This allows them to make informed decisions on whether the interventions should be implemented under programmatic conditions and what adaptions will it need to make it appropriate for the context. The addition of a health economic component to an MDR-TB trial was novel. Therefore, the economic methodology developed in paper 1 was used in other TB work, namely the ShORRT research package[59] developed by WHO in collaboration with LR and aimed to generate data, including economic data, on all-oral shorter treatments that are harmonised across different implementation settings; similar methodology was also used in the second stage of the trial (paper 3).

Two types of economic evaluations (cost-effectiveness and cost-utility) were used for the first time in an MDR-TB treatment trial (in paper 2). The outcome measure for the cost-effectiveness analysis was the

favourable outcome from the trial (a composite outcome) and the QALY for the cost-utility analysis. The composite outcome included both bacteriological (failure, reversion, reinfection) and non-bacteriological unfavourable events (deaths, changes to the allocated regimen). This composite outcome from the trial did not allow for comparisons across interventions and disease areas and we could not estimate the value policy-makers place on this outcome to be able to assess cost-effectiveness for the different MDR-TB treatment options. Patients with bacteriological unfavourable outcome or changes to the allocated regimen would need either a new course of MDR-TB treatment or XDR-TB treatment if further resistance was acquired during the previous treatment course. Re-treatment can also influence mortality, so to the societal costs we would need to add the monetary value that individuals place on reducing their risk of death (the value of a statistical life). This can then be used as a proxy to estimate the value policy makers place on avoiding an unfavourable outcome. Calculating the value of a statistical life can be done through either revealed preference or stated preference method.[60] Revealed preference infers the value of a statistical life from individuals' behaviour in real-life situations where they face mortality risks.[61] Stated preference directly elicits individuals' preferences and willingness to pay for reducing mortality risks through surveys and hypothetical scenarios.[61] In STREAM, it was difficult to obtain accurate and reliable data for value of statistical life estimation, especially as there were no market transactions revealing individuals' trade-offs between income and mortality risk. It was also considered inappropriate to use general estimates from the literature (as it is the empirically estimated value for Sub-Saharan Africa of 4.5 times the GDP per capita[62]) as the value of statistical life estimates can vary depending on the context and risk being evaluated, across countries and populations due to cultural, social and institutional factors that influence individual preferences for risk reduction. For example, willingness to pay for reducing risks related to health, transportation, or environmental hazards may differ, making it challenging to have a universal value applicable to all situations. To account for this, CEACs were constructed to be able to assess the probability that the study regimen was cost-effective compared to control using a range of WTP thresholds (paper 1 and 3). In STREAM phase 2 (paper 3) we also used QALYs as an outcome (in addition to the composite trial outcome) to be able to report on the patient-reported outcomes of the different MDR-TB regimens that were being tested and to make the results comparable across disease areas. In the absence of country specific WTP cost per QALY thresholds we used some empirically derived, published estimates which might be outdated today. However, results were also presented using CEACs.

Clinical trials use a short time horizon and lack reporting on long-term outcomes. However, I believe that there was no evidence that crude extrapolation would change the results for either paper 1 or paper 3 and contend that the time horizon was sufficiently long to capture any important between arm differences in treatment outcomes, survival, SAEs and thus HRQoL which would be likely to have an effect beyond the 76 weeks follow-up. The empirical results in the cost-utility analysis show no significant between arm differences in HRQoL, or survival/death rates at 76 weeks. Hence, extending the time horizon would not materially change the HRQoL or survival results. The cost-effectiveness analysis uses the favourable/unfavourable clinical outcome at 76 weeks as its endpoint, thus between arm differences at 76 weeks are inherently captured in the CEA analysis. I cannot foresee any reason why a favourable/unfavourable clinical outcome measured at 76 weeks would change with a longer time horizon. This is also why the clinical trial is reporting outcomes at this time point.

With respect to costs, in both the CUA and CEA, any between arm differences within the 76-week timeframe are already captured in the health systems cost. Additionally, any provider costs, which occur due to patients being transferred to the salvage regimen, were captured, and added to the total health

system costs. This included costs that would be incurred, beyond the 76-week timeframe, if the salvage regimen extended beyond the 76-week period.

However, we know that hearing loss is one of the main concerns for injectable-containing treatments. In Paper 1, both treatments contained injectables, with the shorter regimen having a shorter injectable-treatment period. If the longer regimen would result in more hearing loss after treatment end as the exposure to the injectable agent was longer than in the short regimen, the conclusions would not change. In paper 3 I developed a Markov model to explore the lifetime HRQoL impact of the hearing loss by arm observed in the clinical trial and results did not change the conclusions. However, I recognise that this does not capture the wider effects of hearing loss on ability to work (and therefore participants economic outcomes) and plan to conduct further analysis of longer-term costs and outcomes (positive and negative e.g. from SAEs) on participants once follow-up data to week 132 week are available. This longer follow-up period is important (and was extended in response to an FDA requirement) due to evidence from other studies which suggest that bedaquiline use is associated with higher mortality over a longer follow-up period. Importantly, though, the week 76 results did not identify any increased mortality associated with bedaquiline use, and I feel that it would not be appropriate to pre-empt the results of an ongoing clinical trial. However, I am also aware that following patients up beyond the 132 weeks already planned, might not be feasible due to, amongst others, high rates of study attrition due to death or loss to follow-up and high running costs. Although modelling a longer time horizon beyond the trial's measured endpoints increases assumptions and uncertainty, modelling can provide helpful insights into the long-term costs and outcomes if week 132 results show significant changes in survival, recurrence, acquired-resistance rates or SAEs across arms.

Another potential limitation related to hearing loss is that HRQoL data might not have fully captured the impact of the different regimens on hearing loss. However, an EQ-5D-5L bolt-on item has been developed and it should be considered for use in future studies to specifically measure hearing impairment.

I believe that the study population in the STREAM trials is representative of the larger population, so its clinical findings can be extrapolated to the whole population. For this reason, pooled efficacy outcomes from all STREAM countries were used as the main outcome for the CEA. This is because the pooled sample (rather than individual country samples) was powered to show the non-inferiority of the Oral regimen to the Control regimen. It was justifiable to pool efficacy (but not costs) data as were much more likely to be consistent across countries and not affected by context (in the way that costs are: wage differentials, patient management strategies, etc.), while being the closest one can get to what might be the true clinical efficacy under implementation conditions. Moreover, this is consistent with the clinical paper, where the efficacy outcomes were also pooled.

However, as economic data were only collected in some of the trial sites and also because there are expected variations in health care practices, patient flows, treatment delivery strategies and DOT locations as well as the frequency of treatment monitoring visits, generalising the economic results outside the countries we collected economic data in should be done with caution.[65,66] Similarly, it would be difficult to generalise findings from the modelling studies outside the countries they were conducted in as in addition to the above, the frequency of DOT can also differ from country to country. Therefore, it was not considered feasible to pool the economic data. First, the heterogeneity between countries can lead to significant variations in cost and cost-effectiveness estimates, making it challenging to use the

pooled results for individual countries. Second, decision-makers often require economic evidence that is directly applicable to their specific healthcare context. Pooled data may not provide the level of granularity required for such decision-making.

Conducting economic evaluations in LMICs can pose significant challenges. One of the significant limitations in LMICs is the lack of comprehensive and reliable data. Also, the lack of trained personnel in conducting economic evaluations in LMICs may hinder the accurate application of economic measurement tools. It can also be challenging to incorporate local stakeholders' preferences into the decision-making process. In STREAM, we used simplified economic models to assess the regimens being tested. Moreover, data were collected in each country, by local researchers, who have previously been trained in conducting economic evaluations. This assured that an accurate representation of the local practices and costs were included in the analysis. In addition to this, the burden of TB care was also assessed by the patients, through the self-reported measure of quality of life or by reporting changes in income and employment status throughout the study. Incorporating their preferences into the economic evaluation helped ensure that the treatment regimens tested are acceptable and feasible in the local context.[67] Although the in-country economic results are not generalisable to other settings for reasons outlined above, the methods and tools produced and used in STREAM could be adopted and adapted by LMICs to conduct economic evaluations outside of a trial context, especially for monitoring cost-effectiveness under operational conditions once new treatment guidelines are released.

STREAM Stage 1 results presented in paper 1 had a direct impact on policy. Although WHO updated their guidelines on MDR-TB treatment in 2019 (recommending a 9-month injectable-containing regimen) before STREAM Stage 1 trial data were publicly available (presented in paper 1), it was our consultation (and that of clinical trial team) and data sharing with WHO that made the shortened regimen to remain a recommended option for some MDR-TB patients. It is too early to say whether paper 2 and 3 results will have an impact on global policy. The results have been presented to WHO and there is an ongoing engagement with UK government interest groups (i.e. All Parliamentary Party Group (APPG) on TB), patient advocacy groups and local communities to maximise chances of impact.

Two types of modelling techniques were also used: a DES model and a decision tree to model the use of existing healthcare resources or digital technology to deliver DOT for the short MDR-TB regimens in a patient-centred way. Previous studies[63,64] showed the utility of an operational modelling approach to policy decisions on TB diagnostics and we used the same approach in paper 4. This strengthens the idea that this modelling approach is likely a useful tool to support policy decisions for many health interventions in LMIC, particularly where there are many unknowns. The model can also be used to show the distribution of patients' journeys as they move through the alternative treatment strategies, including for example the range of lengths of their patient journeys and their associated costs. Standard modelling techniques (i.e. decision tree) that have been previously applied in different areas of healthcare decision making were used in paper 5. Both models have the advantage of being populated with gold standard data coming from clinical trials and were the first to explore patient-centred approaches for the short MDR-TB regimens. Several assumptions were made in developing the models that would need to be tested in Phase-IV studies.

There was no transmission component included in any of the models presented in papers 4 and 5. However, the addition of a transmission model is unlikely to have influenced the findings. Previous studies showed that infectiousness of TB patients diminishes rapidly once effective treatment is

initiated.[68,69] While patients would still be able to transmit TB if they are lost to follow-up and not on treatment, the models assumed that the alternative treatment delivery strategies (that do not require hospitalisation at treatment initiation) had the same loss-to-follow-up rates (as the current standard of care) and that loss-to-follow-up happened at the same time point during treatment. This means that there would be no difference in transmission resulted from loss-to-follow-up between the different treatment delivery strategies.

Patient-centred programmes, which have been proposed in both paper 4 and 5, can improve case detection rates, continuity of care and treatment outcomes, which would in turn reduce transmission, and possibly costs when compared to standard of care. This would make the patient-centred strategies proposed more attractive than in the base case presented in papers 4 and 5. Moreover, there is some evidence that centralised, hospital care (represented by the standard of care in papers 4 and 5) can be a barrier to treatment adherence, that can increase transmission.[70]

3. Conclusions and future studies

The health economic component of the STREAM trial, presented in papers 1, 2 and 3 provide, for the first time, detailed comparative information on the costs faced by health systems treating MDR-TB patients and patients undergoing treatment. This represents a big step forward in the information available to decision makers, being crucial for health policy and practice decisions about uptake and implementation of the shorter regimens. National policy makers need to consider and acknowledge the importance of economic evaluations for MDR-TB treatment and translate this evidence into policy. Further studies should also include local health economists and policy makers to conduct high quality research and aid findings interpretation.

As endorsed by WHO in 2019, we recommended that countries should consider adopting the 9-month injectable-containing regimen for the treatment of MDR-TB. The subsequent evaluations of a novel 9-month all-oral regimen suggested that this was not cost-effective and that its implementation would require additional resource allocation to treat MDR-TB. This would place a huge financial burden on the healthcare systems and national budgets, probably leading to a reduction in number of patients treated if budgets are fixed. However, the economic analysis also showed that a reduction in bedaquiline pricing, the most expensive drug of the regimen, would make the regimen cost-effective in certain settings suggesting that efforts to reduce bedaquiline prices should be stepped up. We found that the 6-month injectable-containing regimen was cost-effective, however, given concerns that the injectable agent can cause hearing loss which represents an important cause of disability, this strategy is unlikely to be attractive to policymakers. The value policy-makers place on avoiding an unfavourable outcome could not be assessed and further research would be required to determine what this value should be, such as a model-based analysis of the costs and consequences following this unfavourable outcome as defined in STREAM. Further analysis of longer-term costs and outcomes on participants will be conducted when week 132 data from the clinical trial are available. A very recent phase II-III trial showed that a 6-month all-oral regimen had higher favourable outcomes when compared to SOC, which is potentially a more attractive alternative. This needs to be evaluated against the other available regimens to explore the complex trade-offs between costs, treatment efficacy and frequency and severity of SAEs.

Paper 1 and paper 3 also reported that most participants experienced catastrophic costs, however, in addition to the studies presented here we need qualitative data to better understand their drivers.

Catastrophic costs can have wide-ranging consequences for TB transmission, adherence and treatment outcomes and designing proper care packages to avoid them is essential to achieving global targets for ending TB. I have therefore developed a qualitative study to help us gain a better understanding on the opinions, motivations and drivers behind patients' behaviour. This study has already been conducted and I am currently analysing the responses.

Patient-centred DOT delivered either by health workers (paper 4), family or with the use of digital technologies (paper 5) can reduce patient costs and overall societal costs. This underpins WHO recommendation to prioritise a greater move towards patient-centred care with supporting implementation research. Apart from reducing the costs for both the health system and patients, patient-centred DOT strategies can have wider implications such as increased treatment access and completion rates. Paper 4 and paper 5 will need updating when data on the efficacy of the different treatment support strategies will be available. Further studies in other countries should make efficacy availability data a priority, especially as new strategies for delivering treatment are being developed. Phase-IV studies would be best suited to generate specific data on the efficacy of these DOT delivery methods. The impact of such studies will be crucial to support future policy decisions.

One common topic across all papers presented in this thesis are the magnitude and source of patient costs. It showed that, despite TB treatment being 'free', patients spend important amounts of money on supplementary food expenditure, transport for travelling to and from the health facility, while also experiencing income loss. These findings should be used to inform social protection measures for TB-affected households to mitigate financial shock and improve TB outcomes. They can contribute to interrupting the TB poverty cycle by designing and implementing financial interventions and food support programmes. Financial interventions such as cash transfers are usually designed to prevent out-of-pocket costs and lost income while seeking TB care. They can be given conditional on treatment adherence or other relevant health behaviours and target communities with high levels of TB. The findings presented in this thesis can be used to inform the amount and timing of cash transfers required to enable people to cope with and recover from adversities. Similarly, as most patients reported buying supplementary food, they can help designing the magnitude of food support offered to alleviate food insecurity and malnutrition. Also, as showed in papers 4 and 5, delivering MDR-TB treatment using patient-centred approaches, that include digital technologies where these are available, can reduce patient costs and the percentage of patients experiencing catastrophic costs. However, these measures will need to be tested using pragmatic trials, implementation trials or mixed-methods studies- essential for assessing feasibility and impact of social protection programs.

While the papers presented here focus on the economics of MDR-TB treatment regimens and delivery strategies, it is important to note that many of those who complete TB treatment experience long-term morbidity, including post-TB lung disease and difficulty in recovering income and employment[71]. Some of these have been captured in papers 1 and 3, as patients were followed up for 92 weeks and 36 weeks after treatment end, respectively and costs and quality of life (in paper 3 only) reported. Patients in paper 3 were also followed up for 92 weeks after treatment end and these results will be reported separately, together with a decision tree model that will extrapolate results beyond trial end and will explore the long-term morbidity of TB, and the associated costs. However, longer-term follow-up studies that track TB patients for an extended period after treatment end are needed. The longer-term follow-up STREAM analysis is undergoing, and the results will be able to provide insights into the long-term TB or TB treatment-associated morbidity, costs and healthcare needs post treatment. This

knowledge can inform evidence-based interventions and policies aimed at reducing the burden of post-TB complications, enhancing patient well-being, financial recovery and optimizing the allocation of healthcare resources in the post-treatment phase. Extended cost-effectiveness analysis (that also includes non-health benefits such as financial risk protection and equity) can then assess the health and financial impact of the policies and whether they reached their target.

Considering the limitations in global healthcare budgets, determining the most effective allocation of resources is paramount. Tackling TB requires a multi-faceted approach, with both clinical and economic evidence needed to inform the decision-making process.

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Appendices

1. List of all publications by candidate

de Siqueira Filha, N.T., Li, J., Phillips-Howard, P.A., Quayyum, Z., Kibuchi, E., Mithu, M.I.H., Vidyasagaran, A., Sai, V., Manzoor, F., Karuga, R., Awal, A., Chumo, I., Rao, V., Mberu, B., Smith J., Saidu, S., Tolhurst, R., Mazumdar, S., **Rosu, L.**, Garimella, S. and Elsey, H., 2022. The economics of healthcare access: a scoping review on the economic impact of healthcare access for vulnerable urban populations in low-and middle-income countries. *International journal for equity in health*, *21*(1), p.191.

Jarde, A., Ma, R., Todowede, O.O., Latif, A., Yaqoob, A., Afaq, S., Ferdous, T., Tomeny, E.M., **Rosu, L**., Mrema, L.E. and Rakhshanda, S., 2022. Prevalence, clusters, and burden of complex tuberculosis multimorbidity in low-and middle-income countries: a systematic review and meta-analysis. *medRxiv*, pp.2022-09.

Karanja, S., Malenga, T., Mphande, J., Squire, S.B., Chakaya Muhwa, J., Tomeny, E.M., **Rosu, L.**, Mulupi, S., Wingfield, T., Zulu, E. and Meghji, J., 2022. Stakeholder perspectives around post-TB wellbeing and care in Kenya and Malawi. *PLOS Global Public Health*, *2*(9), p.e0000510.

Hardy, A., Proctor, M., MacCallum, C., Shawe, J., Abdalla, S., Ali, R., Abdalla, S., Oakes, G., **Rosu, L**. and Worrall, E., 2022. Conditional trust: Community perceptions of drone use in malaria control in Zanzibar. *Technology in Society*, *68*, p.101895.

2. The papers presented in this paper

Economic evaluation of short treatment for multidrug-resistant tuberculosis, Ethiopia and South Africa: the STREAM trial

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Objective To investigate cost changes for health systems and participants, resulting from switching to short treatment regimens for multidrug-resistant (MDR) tuberculosis.

Methods We compared the costs to health systems and participants of long (20 to 22 months) and short (9 to 11 months) MDR tuberculosis regimens in Ethiopia and South Africa. Cost data were collected from participants in the STREAM phase-III randomized controlled trial and we estimated health-system costs using bottom-up and top-down approaches. A cost–effectiveness analysis was performed by calculating the incremental cost per unfavourable outcome avoided.

Findings Health-care costs per participant in South Africa were 8340.7 United States dollars (US$) with the long and US$ 6618.0 with the short regimen; in Ethiopia, they were US$ 6096.6 and US$ 4552.3, respectively. The largest component of the saving was medication costs in South Africa (67%; US$ 1157.0 of total US$ 1722.8) and social support costs in Ethiopia (35%, US$ 545.2 of total US$ 1544.3). In Ethiopia, trial participants on the short regimen reported lower expenditure for supplementary food (mean reduction per participant: US$ 225.5) and increased working hours (i.e. 667 additional hours over 132 weeks). The probability that the short regimen was cost–effective was greater than 95% when the value placed on avoiding an unfavourable outcome was less than US$ 19 000 in Ethiopia and less than US$ 14 500 in South Africa.

Conclusion The short MDR tuberculosis treatment regimen was associated with a substantial reduction in health-system costs and a lower financial burden for participants.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Until recently, guidelines on multidrug-resistant (MDR) tuberculosis recommended a treatment period of 20 to 22 months,[1] which has substantial costs for both patients and health services, particularly for hospitalization.[2–6] A shortened treatment regimen of 9 to 11 months was tested in Bangladesh in 2010, with promising efficacy, and was subsequently implemented in several West African countries.[7] However, no randomized controlled trials or economic evaluations have been performed. Given that health systems in many countries with a high MDR tuberculosis burden face resource constraints,[5] there have been calls for more research on the economic impact of MDR tuberculosis. Moreover, global policy goals emphasize financial protection for patients and the elimination of catastrophic health-care costs.[8]

The results of the phase-III, noninferiority, randomized, controlled trial, STREAM, were published in 2019. They demonstrated that a short MDR tuberculosis regimen of 9 to 11 months had noninferior efficacy and comparable safety to the World Health Organization's (WHO's) approved standard regimen of 20 to 22 months (i.e. the long regimen).[9] The trial collected data on the costs of each regimen for participants and health systems and on participants' financial wellbeing.[10,11] Our aim was to investigate the nature, magnitude and timing of the changes in costs for participants and health systems that result from switching to the short MDR tuberculosis regimen. As WHO's treatment guidelines are undergoing rapid revision,[12] we hope that our overall cost–effectiveness assessment and detailed cost analysis will help tuberculosis programme organizers to understand the potential costs and savings of transitioning to all-oral, short treatment regimens and to devise detailed plans for their implementation.

Methods

The STREAM trial's economic evaluation compared the health-system and participant costs of short and long regimens for treating MDR-TB in Ethiopia and South Africa. Before the trial, the median treatment duration was 20 months in Ethiopia and 22 months in South Africa. Trial participants were randomly assigned in a 2 : 1 ratio to the short or long regimen, with randomization stratified by trial site and the presence of human immunodeficiency virus infection.[11] Data were collected at two sites in Ethiopia (i.e. St Peter's Specialized Hospital and the Armauer Hansen Research Institute Hospital, both in Addis Ababa) and two in South Africa (i.e. Sizwe Tropical Diseases Hospital in Johannesburg and Doris

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Goodwin Hospital in Pietermaritzburg). Details of the methods are available elsewhere.[11,13]

We estimated health-system costs using a mix of bottom-up and top-down approaches.[14,15] The costs of medications, inpatient stays and serious adverse events were calculated for individuals and the costs of laboratory tests, electrocardiography, staff time, consumables and social support were based on aggregate data collected during the trial. Where trial data were insufficiently detailed, we obtained supplementary information on typical care activities, such as tuberculosis drug use and the resources involved, by reviewing national and local guidelines and by interviewing clinical and managerial staff.[10] We estimated costs using relevant unit costs for each country (available in the data repository).[13]

At some trial sites, participants were hospitalized from treatment initiation until they were smear negative. As accurate records of admission and discharge dates were unavailable, we used the time to sputum smear conversion as a proxy for the inpatient stay, allowing an additional 4 weeks for the result to be confirmed and communicated to clinicians. If a participant died within this period or before smear conversion, we assumed the hospital stay was the number of treatment days.

We also estimated the health-care resources required to manage serious adverse events because these events were the most costly.[16] We estimated these costs for Ethiopia and based them on a sample of all serious adverse events associated with MDR tuberculosis or its treatment.[13] Tests, examinations and care activities relating to the diagnosis and management of these events were identified by interviewing clinical staff and reviewing case notes.

Data on costs incurred by participants and on their socioeconomic status were collected at scheduled assessments between November 2012 and December 2017 in Ethiopia and between August 2014 and January 2018 in South Africa. The questionnaires used to assess participants' costs were developed in English from the STOP-TB Partnership's questionnaire,[17] translated into local languages (i.e. Amharic, Zulu and Sesotho) and administered by the same staff who collected clinical data from trial participants. The questionnaires were administered 12 weeks after treatment randomization and every 12 weeks thereafter until the end of follow-up (i.e. 132 weeks). Information was collected on direct costs (e.g. food and transport) and indirect costs (e.g. lost income) incurred during the preceding 12 weeks. Participants were asked to estimate costs they would expect to face in routine care: for example, in South Africa, as free transport was provided for STREAM participants to attend clinic reviews, they were asked to estimate the usual cost of these trips. A separate questionnaire on participants' socioeconomic characteristics was administered at randomization and then every 24 weeks. The number of participants at each site who provided data on direct costs, the cost of supplementary food and the number of hours worked is presented in Table 1.

Table 1. **Participants providing information on direct costs of multidrug-resistant tuberculosis treatment, STREAM trial, Ethiopia and South Africa, 2012–2018**

Information provided	No. of participants			
	Ethiopia		South Africa	
	St Peter's Specialized Hospital (*n* = 68)	Armauer Hansen Research Institute Hospital (*n* = 51)	Doris Goodwin Hospital (*n* = 14)	Sizwe Tropical Diseases Hospital (*n* = 33)
Direct costs of visiting health facility	65	46	14	18
Cost of supplementary food at treatment week:				
12	35	20	9	2
24	50	25	12	5
36	48	26	13	6
48	53	22	13	2
60	57	30	0	0
72	59	36	0	0
84	54	38	11	3
96	48	35	4	7
108	50	42	2	2
120	49	41	6	2
132	61	39	14	0
No. of working hours at treatment week:				
24	56	26	11	6
48	56	30	13	9
72	53	37	13	6
96	39	38	5	0
120	47	41	6	0
132	60	38	0	5

STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis.

The study was approved by the International Union Against Tuberculosis and Lung Disease's ethics advisory group, the South African Medical Research Council's ethics committee, the Wits Health Consortium's protocol review committee, the University of the Witwatersrand's human research ethics committee, the University of Kwazulu–Natal's biomedical research ethics committee, the St Peter TB Specialized Hospital's ethical review committee and the Armauer Hansen Research Institute–All Africa Leprosy Rehabilitation and Training Hospital's ethical review committee. All participants provided written informed consent. The trial registration number is ISRCTN78372190.

Analysis

We estimated costs in 2017 United States dollars (US$) from the perspective of the health system and the participant separately.[18] A trial-based perspective was adopted for estimating participants' costs with a 132-week time horizon. Health-system costs were calculated for

each participant who completed treatment – no follow-up costs were included because patients were not routinely followed up after the end of treatment. The cost of activities judged by the study's clinical experts to have been solely for research (e.g. taking samples for pharmacokinetic studies) were excluded.

A cost–effectiveness analysis was performed by calculating the incremental cost per unfavourable outcome avoided, which was the primary efficacy outcome of the STREAM trial. Unfavourable outcomes were defined as: (i) starting two or more drugs not in the allocated regimen; (ii) extending treatment beyond its scheduled end for any reason other than compensating for treatment not taken (up to a maximum of 8 weeks); (iii) death from any cause; (iv) a positive culture result when the patient was last seen; and (v) not seen at 76 weeks or later.[9] Decision uncertainty was captured by conducting a probabilistic sensitivity analysis, which involved representing all uncertain parameters as probability distributions and propagating uncertainty using Monte Carlo simulations.[19] The analysis was performed for Ethiopia and South Africa. Bootstrapping was used to account for uncertainty in parameters. We simulated 1000 estimates of mean costs and outcomes, which were used to construct 1000 simulated cost–effectiveness ratios. The results of the probabilistic sensitivity analysis are depicted in cost–effectiveness acceptability curves,[20] which show the proportion of simulation results in which the short regimen was cost–effective. We assessed cost–effectiveness using a range of willingness-to-pay thresholds, which are payment thresholds that a decision-maker might assign to avoiding an unfavourable MDR tuberculosis outcome. We considered willingness-to-pay thresholds up to US$ 100 000 for both Ethiopia and South Africa.

Health-system costs

In Ethiopia, the cost of an inpatient stay was the sum of: (i) ward staff costs; (ii) inpatient overhead costs, which included hospital administration costs; and (iii) a fixed hotel cost, which included the cost of a bed, basic supplies and meals. For the two trial sites in Ethiopia, inpatient overhead costs were estimated using facility financial records. In South Africa, we based the estimates of basic inpatient unit costs on a published study.[3] We judged this source to be the most appropriate as data were collected from a referral hospital similar in size to the two hospitals involved in the STREAM trial. A sensitivity analysis was carried out to explore how total costs would vary if unit costs from other studies were applied.[4,21,22]

Participant costs

We estimated the mean cost of a single health facility visit from participant-reported direct costs. The total cost incurred in routine practice was calculated by multiplying this mean by the number of visits expected during usual clinical management. For Ethiopia, missing values in participants' responses were imputed using chained multiple imputation as the reference case.[23] Two response categories included imputed values: (i) expenditure on supplementary food; and (ii) hours worked.[13] Chained imputations could not be performed for South Africa because of a lack of data on both the imputed values and the variables included in the imputation model. All analyses of participants' cost were performed in Stata v.15.1 (StataCorp LP., College Station, United States of America). Treatment of MDR tuberculosis involves an intensive phase (when five antibiotics are given daily, including an injectable) followed by a continuation phase (when at least four antibiotics are given orally). The intensive phase is costlier for patients because health facility visits are needed for the injections. There is also a greater risk of medication side-effects in this phase.

Results

Health-system costs

Table 2 gives details of the health-system costs for the short and long MDR tuberculosis treatment regimens. The cost was greater with the long than the short regimen: the total cost per participant in Ethiopia was US$ 6096.6 versus US$ 4552.3 (25% difference) for the two regimens, respectively, and in South Africa, US$ 8340.7 versus US$ 6618.0 (21% difference), respectively. Overall, 61% (US$ 944.3) of the reduction occurred in the continuation phase in Ethiopia, as did 85% (US$ 1461.3) in South Africa. In Ethiopia, the saving was primarily due to lower costs for social support (35%; US$ 545.2), laboratory tests (30%; US$ 456.9) and medications (20%; US$ 301.7), whereas in South Africa, the reduction was primarily due to lower medication (67%; US$ 1157.0) and staff costs (36%; US$ 619.1; Table 2). For the short regimen, the cost of cardiac monitoring per participant was US$ 149.5 in Ethiopia and US$ 150.9 in South Africa.

In Ethiopia, there was no substantial difference in the mean medication cost per participant between the regimens: it was US$ 1361.3 (95% confidence interval, CI: 1255.7 to 1465.8) for the short regimen and US$ 1663.0 (95% CI: 1536.4 to 1790.4) for the long regimen. In South Africa, however, there was a significant difference: the mean medication cost per participant was US$ 433.9 (95% CI: 385.4 to 481.1) for the short regimen and US$ 1590.9 (95% CI: 1283.5 to 1899.3) for the long regimen.

The largest expenditure category for both regimens was inpatient costs, even when the unit cost was varied in a sensitivity analysis.[13] In Ethiopia, the mean inpatient stay was 9.62 weeks (95% CI: 9.01 to 10.24) for the short regimen and 9.64 weeks (95% CI: 8.74 to 10.52) for the long regimen. In South Africa, it was 9.43 weeks (95% CI: 8.30 to 10.56) for the short regimen and 9.02 weeks (95% CI: 7.51 to 10.52) for the long regimen. Consequently, changing to the short regimen had no meaningful implication for inpatient costs. The mean cost of a serious adverse event in Ethiopia was higher for the long (US$ 82.1; 95% CI: 46.0 to 118.2) than the short regimen (US$ 15.7; 95% CI: 1.2 to 30.2; Table 2). Although each episode was expensive to treat, the cost of serious adverse events did not substantially influence cost savings with the short regimen as few participants experienced them.

Our probabilistic sensitivity analysis showed that the short regimen is highly likely to be cost–effective (Fig. 1 and Fig. 2). However, the probability it would be cost–effective declined as the value decision-makers placed on avoiding an unfavourable outcome increased: the probability was greater than 95% if that value were less than US$ 19 000 in Ethiopia and less than US$ 14 500 in South Africa. Even when the value was as high as US$ 100 000, the probability was still above 77% for both countries.

Participant costs

Data for the participant-perspective analysis were available from 111 trial participants in Ethiopia and 14 in South Africa (Doris Goodwin Hospital). The mean cost per participant of a health facility visit was US$ 1.1 in Ethiopia

Table 2. **Health-system costs of short and long multidrug-resistant tuberculosis treatment, STREAM trial, Ethiopia and South Africa, 2012–2018**

Cost element, by country	Health-system costs in US$ per patient (% of country total)						Difference in health-system costs between long and short regimens in US$ per patient (% of country total)[b]		
	Long regimen[a]			Short regimen[a]					
	Intensive phase[c]	Continuation phase[c]	Total for two phases	Intensive phase[c]	Continuation phase[c]	Total for two phases	Intensive phase[c]	Continuation phase[c]	Total for two phases
Ethiopia									
Inpatient stay	2090.1 (50)	0.0 (0)	2090.1 (34)	2087.7 (59)	0.0 (0)	2087.7 (41)	2.4 (< 1)	0.0 (0)	2.4 (< 1)
Laboratory tests	381.0 (9)	469.6 (24)	850.6 (14)	197.2 (6)	196.5 (20)	393.7 (10)	183.8 (30)	273.1 (29)	456.9 (30)
Cardiac safety monitoring	0.0 (0)	0.0 (0)	0.0 (0)	79.8 (2)	69.8 (7)	149.6 (3)	−79.8 (−13)	−69.8 (−7)	−149.6 (−10)
Medication	1153.9 (28)	509.1 (27)	1663.0 (27)	969.5 (27)	391.8 (40)	1361.3 (33)	184.4 (32)	117.3 (12)	301.7 (20)
Staff	98.5 (2)	104.7 (5)	203.2 (4)	62.7 (2)	43.6 (4)	106.3 (3)	35.8 (6)	61.1 (7)	96.9 (6)
Social support	218.1 (5)	581.5 (30)	799.6 (13)	72.7 (2)	181.7 (19)	254.4 (6)	145.4 (24)	399.8 (42)	545.2 (35)
Consumables	163.2 (4)	244.8 (13)	408.0 (7)	81.6 (2)	102.0 (10)	183.6 (4)	81.6 (13)	142.8 (15)	224.4 (15)
Serious adverse events	60.5 (2)	21.6 (1)	82.1 (1)	14.1 (< 1)	1.6 (< 1)	15.7 (< 1)	46.4 (8)	20.0 (2)	66.4 (4)
Total	4165.3 (100)	1931.3 (100)	6096.6 (100)	3565.3 (100)	987.0 (100)	4552.3 (100)	600.0 (100)	944.3 (100)	1544.3 (100)
South Africa									
Inpatient stay	4284.5 (70)	0.0 (0)	4284.5 (51)	4480.2 (77)	0.0 (0)	4480.2 (68)	−195.7 (−74)	0.0 (0)	−195.7 (−11)
Laboratory tests	459.5 (8)	452.9 (20)	912.4 (11)	452.7 (8)	279.1 (35)	731.8 (11)	6.8 (3)	173.8 (12)	180.6 (10)
Cardiac safety monitoring	0.0 (0)	0.0 (0)	0.0 (0)	71.0 (1)	79.9 (10)	150.9 (2)	−71.0 (−27)	79.9 (−6)	−150.9 (−9)
Medication	621.0 (10)	969.9 (43)	1590.9 (19)	260.0 (4)	173.9 (22)	433.9 (6)	361.0 (138)	796.0 (54)	1157.0 (67)
Staff	643.6 (11)	692.5 (31)	1336.1 (16)	500.6 (9)	216.4 (28)	717.0 (11)	143.0 (55)	476.1 (33)	619.1 (36)
Social support[d]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Consumables	78.2 (1)	138.6 (6)	216.8 (3)	60.8 (1)	43.3 (5)	104.1 (2)	17.4 (7)	95.3 (7)	112.7 (7)
Total	6086.8 (100)	2253.9 (100)	8340.7 (100)	5825.3 (100)	792.7 (100)	6618.0 (100)	261.5 (100)	1461.3 (100)	1722.8 (100)

STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis; US$: United States dollar.

[a] The long regimen lasted 20 to 22 months and the short regimen lasted 9 to 11 months.

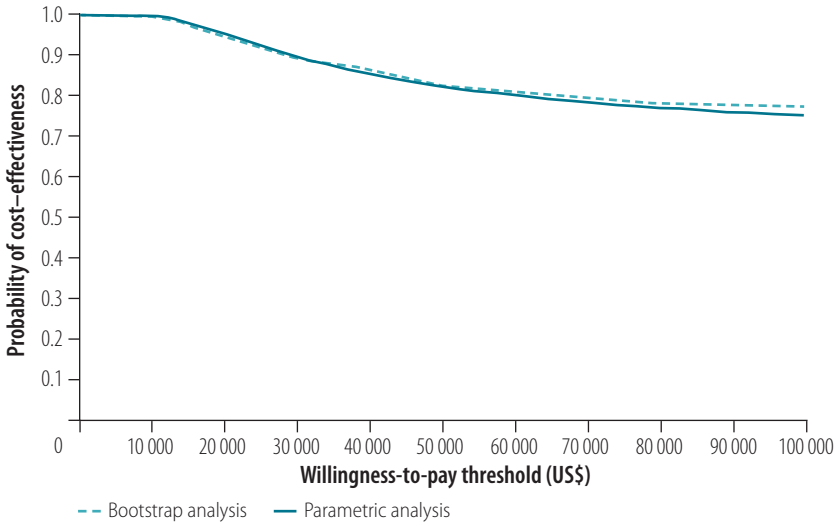
[b] Negative values indicate that costs were greater for the short than the long regimen.

[c] In the intensive phase, five antibiotics are given daily (including an injectable); in the subsequent continuation phase, at least four antibiotics are given orally.

[d] In South Africa, the cost of social support to the health system was zero because, unlike in Ethiopia, social support in South Africa was covered by donor funding.

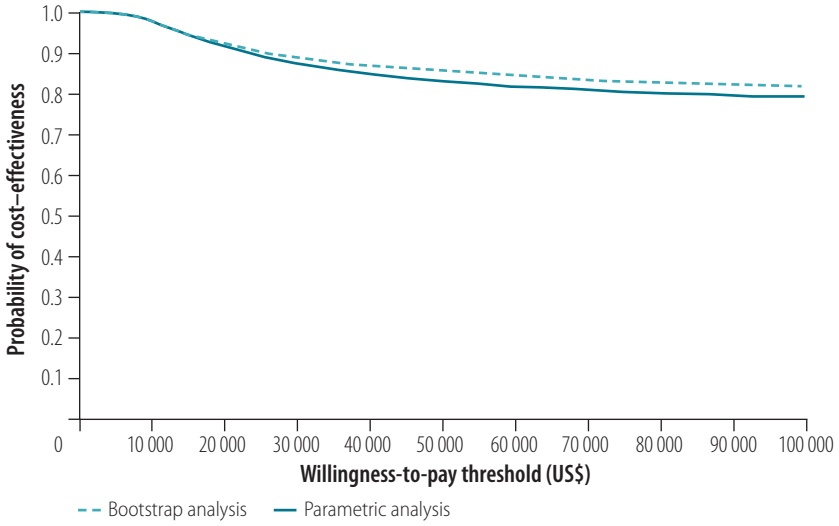
Note: In South Africa, we were unable to estimate the cost of serious adverse events because care records were not available.

Fig. 1. **Probability that short multidrug-resistant tuberculosis treatment was more cost–effective than long treatment, by willingness to pay to avoid unfavourable outcomes, STREAM trial, Ethiopia, 2012–2017**



STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis; US$: United States dollar.
Notes: Long treatment lasted 20 to 22 months and short treatment lasted 9 to 11 months. The willingness-to-pay threshold is the amount a decision-maker would pay to avoid an unfavourable outcome due to multidrug-resistant tuberculosis. For the parametric analysis, parameter values were simulated from distributions derived from the summary statistics of the observed data. For the bootstrap analysis, data were sampled with replacement values from the STREAM data set.

Fig. 2. **Probability that short multidrug-resistant tuberculosis treatment was more cost–effective than long treatment, by willingness to pay to avoid unfavourable outcomes, STREAM trial, South Africa, 2014–2018**



STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis; US$: United States dollar.
Notes: Long treatment lasted 20 to 22 months and short treatment lasted 9 to 11 months. The willingness-to-pay threshold is the amount a decision-maker would pay to avoid an unfavourable outcome due to multidrug-resistant tuberculosis. For the parametric analysis, parameter values were simulated from distributions derived from the summary statistics of the observed data. For the bootstrap analysis, data were sampled with replacement values from the STREAM data set

(US$ 0.8 for transport and US$ 0.4 for food) and US$ 4.9 in South Africa (US$ 3.6 for transport and US$ 1.3 for food). In Ethiopia, as the short regimen was 11 months shorter than the long regimen, the cost saving per participant was US$ 12.5 over the treatment course. In South Africa, the difference was 13 months, giving a saving of US$ 64.0.

In Ethiopia, 94% (104/111) of participants reported spending on supplementary food (e.g. meat, fruit and energy drinks). The cumulative mean per participant was US$ 549.1 (95% CI: 426.7 to 671.6) for the long regimen and US$ 323.6 (95% CI: 250.6 to 396.7) for the short regimen; the difference was US$ 225.5 (95% CI: 133.0 to 297.1; Fig. 3). The total direct costs per participant were US$ 575.4 for the long regimen and US$ 337.3 for the short regimen. Consequently, the total direct cost saving per participant with the short regimen was US$ 238.0, of which 95% related to reduced spending on supplementary food.[13]

Participants in Ethiopia were unable or unwilling to provide estimates of their typical monthly income. However, many reported the number of hours they were able to work (Fig. 4). By 48 weeks after treatment initiation, an estimated 52% of participants on the short regimen were able to work at least 8 hours per day compared with 30% on the long regimen. Overall, the mean additional time worked per participant on the short regimen during the 132 weeks of treatment and follow-up was 667 hours (95% CI: 193 to 1127). This increase in productivity corresponded to a saving in indirect costs of US$ 175.7 per participant based on the reported incomes of MDR tuberculosis patients in Ethiopia.[24] Consequently, the total cost saving per participant in Ethiopia was US$ 413.7 – 42% related to indirect costs and 58% related to direct costs. Insufficient data were available to estimate supplementary food expenditure and hours worked by participants in South Africa.[13]

Discussion

Using data from the phase-III, randomized, controlled STREAM trial, we found that the short regimen of MDR tuberculosis treatment led to substantial savings for both participants and the health-care system. Although this was intuitively expected, there were important, unexpected findings on the timing and drivers of

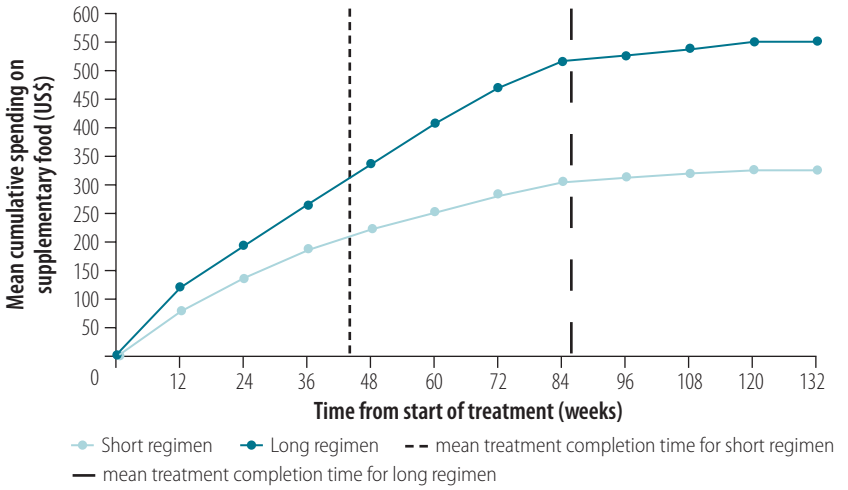
these savings. We found that participant cost savings in Ethiopia were mainly due to lower expenditure on supplementary food and increased working hours; savings from fewer health facility visits were less important. The increase in working hours accrued largely between treatment weeks 16 and 32, when participants on the long regimen were receiving injectable drugs and those on the short regimen were not. Supplementary food expenditure diverged largely during weeks 48 to 84, when only those on the long regimen were still receiving treatment. These may be crucial benefits for MDR tuberculosis patients and their families given their typical socioeconomic situation. We estimated the mean cost to all trial participants in Ethiopia was 30 to 50% of their income,[24] suggesting that a substantial number experienced catastrophic costs, though many fewer on the short regimen were affected.

Clinical and health-system factors, such as wages, prices and models of care, can also influence savings. For example, if inpatient care were maintained while patients receive injectable medications, switching to the short regimen (which involves four fewer weeks of injectable therapy) in South Africa would result in an additional saving of US$ 1958 per patient, thereby increasing the total saving to US$ 3681 per patient. We also estimated the effect on health-system costs in South Africa if outpatient care were the norm, which is increasingly common.[25,26] Using published outpatient unit costs,[3] the total health-system costs of the long and short regimens would be US$ 5600 and US$ 3415 per patient, respectively, both substantially less than for inpatient care (Table 2).

Cost savings also depended on the choice of antibiotics. In South Africa (but not Ethiopia), terizidone was used in the long regimen, whereas the medications used in the short regimen were heavily regulated, which gave substantial cost savings. Although participants on the short regimen needed cardiac monitoring due to the increased risk of a prolonged QTc interval, the cost of US$ 150 per participant was greatly outweighed by other savings.

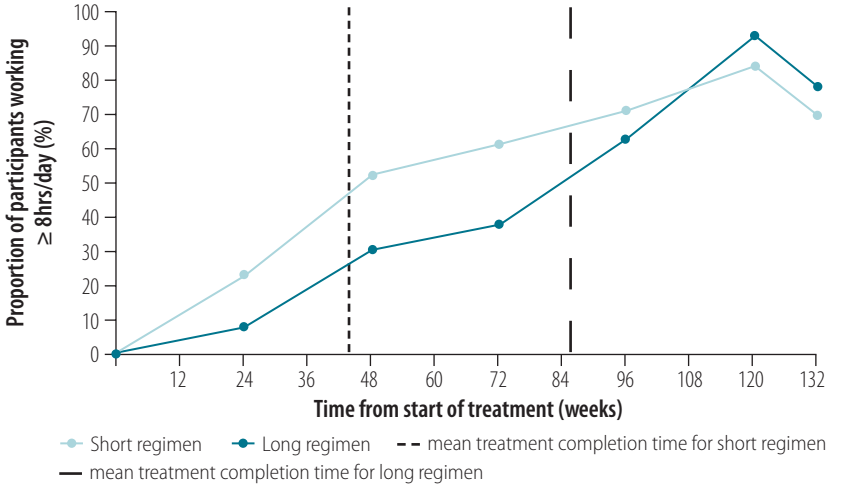
Our study has limitations. Considerable data on participants' responses were missing, particularly from South Africa where operational problems delayed data collection and reduced participants' willingness to provide economic data. However, sensitivity analyses showed that these missing data had little impact on our findings.[13] Moreover, the experience of trial participants was different from that of patients seen in routine practice, which could have influenced costs: the number of visits was different, and some support was provided (e.g. free or subsidized transport). Where possible, we adjusted our analysis to account for such differences. We did not include the costs or consequences of treatment failure, such as retreatment or increased morbidity and mortality. Short regimens could lead to an increased likelihood of retreatment or to more extensive drug resistance. However, no significant difference in unfavourable outcomes between the regimens was observed.

Fig. 3. **Participants' cumulative spending on supplementary food, by length of multidrug-resistant tuberculosis treatment, STREAM trial, Ethiopia, 2012–2017**



STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis; US$: United States dollar.
Notes: The long regimen lasted around 86 weeks and the short regimen lasted around 44 weeks. The dots represent data collection times. The nearest data collection time after completion of the short regimen was in week 48 and the nearest time after completion of the long regimen was in week 96.

Fig. 4. **Proportion of participants working at least 8 hours per day, by length of multidrug-resistant tuberculosis treatment, STREAM trial, Ethiopia, 2012–2017**



STREAM: standard treatment regimen of antituberculosis drugs for patients with multidrug-resistant tuberculosis.
Notes: Work included schooling, housework and formal and informal work. The long regimen lasted around 86 weeks and the short regimen lasted around 44 weeks. All participants were hospitalized at randomization to treatment regimen. The percentages have been imputed as described in the methods section.

One limitation of our cost–effectiveness analysis is that we cannot definitively assert that the short regimen is cost–effective because the precise value placed on avoiding unfavourable outcomes was not available. Further research is needed to determine this value, which would involve estimating the costs and consequences of unfavourable outcomes. Nevertheless, the value would have to be hundreds of thousands of dollars before the short regimen becomes unlikely to be cost–effective.

In South Africa, we were unable to estimate the cost of serious adverse events because care records were not available. However, given the marginal difference in serious adverse events rates between regimens,[9] it is unlikely they would have meaningfully changed our findings. Serious metabolic and nutritional disorders were more frequent in Ethiopia than in the trial overall (29%; 12/41, versus 9%; 12/141, respectively),[9] probably because the injectable drug used was capreomycin, which has more metabolic side-effects than the kanamycin and amikacin used at other sites.

Despite these limitations, our study provides detailed comparative information on the health-system costs of treating MDR tuberculosis patients with different regimens. Furthermore, we found that the short regimen is associated with substantial savings for the health system, which are influenced by the local model of care. Nevertheless, the short regimen is highly likely to be cost–effective in other low- and middle-income countries. In addition, participants were able to return to work sooner, thereby helping safeguard the financial wellbeing of their households.

New evidence on the efficacy of short, all oral regimens for MDR tuberculosis will influence WHO's considerations on whether to recommend a transition away from long regimens and the use of injectables.[12] As we demonstrated, the economic implications of short regimens will vary considerably between countries. These variations are unlikely to change the overall economic case for shorter regimens, but they will be important for optimizing implementation. The switch to shorter regimens will involve stakeholders examining the local importance of the different cost categories we investigated in Ethiopia and South Africa and reflecting on their relevance for estimating budgets and developing implementation plans. ■

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Competing interests: None declared.

ملخص

التقييم الاقتصادي للعلاج القصير لمرض السل المقاوم للأدوية المتعددة، إثيوبيا وجنوب أفريقيا: تجربة STREAM

الغرض استقصاء التغيرات في تكلفة النظم الصحية والمشاركين، الناتجة عن التحول إلى نظم العلاج القصير للسل المقاوم للأدوية المتعددة.

الطريقة قمنا بالمقارنة بين تكاليف النظم الصحية والمشاركين في نظم العلاج الطويلة (20 إلى 22 شهرًا)، والقصيرة (9 إلى 11 شهرًا) للسل المقاوم للأدوية المتعددة في إثيوبيا وجنوب أفريقيا. تم جمع البيانات الخاصة بالتكلفة من المشاركين في المرحلة الثالثة من تجربة STREAM العشوائية الخاضعة للتحكم، وقدرنا تكاليف النظام الصحي باستخدام أساليب عملية تتدرج من القاع للقمة ومن القمة للقاع. تم إجراء تحليل فعال من حيث عن طريق حساب التكلفة التزايدية للنتائج غير المرغوب فيها التي تم تجنبها.

النتائج بلغت تكاليف الرعاية الصحية لكل مشارك في جنوب إفريقيا 8340.7 دولاراً أمريكياً (USD) بالنسبة للعلاج الطويل، و6618.0 دولاراً أمريكياً بالنسبة للعلاج القصير؛ في إثيوبيا، وكانت 6096.6 دولاراً أمريكياً و4552.3 دولاراً أمريكياً، على التوالي. كان أكبر مكون للتوفير هو تكاليف الأدوية في جنوب إفريقيا (67%؛ 1157.0 دولاراً أمريكياً من إجمالي 1722.8 دولاراً أمريكياً)، وتكاليف الدعم الاجتماعي في إثيوبيا (35%، 545.2 دولاراً أمريكياً من إجمالي 1544.3 دولاراً أمريكياً). في إثيوبيا، أعلن المشاركون في التجربة على النظام القصير عن انخفاض الإنفاق على الغذاء التكميلي (متوسط الانخفاض لكل المشارك: 225.5 دولاراً أمريكياً) وزيادة ساعات العمل (أي 667 ساعة إضافية عبر 132 أسبوعاً). إن احتمال أن يكون نظام العلاج القصير فعالاً من حيث التكلفة، كان أكبر من 95% عندما كانت القيمة المخصصة لتجنب النتائج غير المرغوبة فيها أقل من 19000 دولار أمريكي في إثيوبيا، وأقل من 14500 دولار أمريكي في جنوب أفريقيا.

الاستنتاج ارتبط نظام العلاج القصير لمرض السل المقاوم للأدوية بتخفيض ملموس في تكاليف النظام الصحي، وانخفاض العبء المالي على المشاركين.

摘要

埃塞俄比亚与南非的短期治疗耐多药结核病经济评估：STREAM 试验

目的 旨在调查因改用耐多药 (MDR) 结核病的短期治疗方案而引起卫生系统和参与者的费用变化。

方法 我们比较了埃塞俄比亚与南非长期（20 至 22 个月）和短期（9 至 11 个月）耐多药结核病治疗方案对卫生系统和参与者产生的费用。费用数据是从 STREAM 第三期随机对照试验的参与者中收集的，并且我们采用自下而上和自上而下的方法估算了卫生系统的费用。通过计算防止不良疗效的人均增量费用进行了费用效益分析。

结果 南非长期参与者的人均医疗护理费用为 8340.7 美元，短期参与者的人均医疗护理费用为 6618.0 美元；埃塞俄比亚长期参与者和短期参与者的人均医疗护理费用分别为 6096.6 美元和 4552.3 美元。南非最大的节省部分是药费（67%；总计 1722.8 美元中达 1157.0 美元），埃塞俄比亚最大的节省部分是社会支持费用（35%，总计 1544.3 美元中达 545.2 美元）。在埃塞俄比亚，短期方案的试验参与者报告补充营养食品的支出减少了（每位参与者平均减少：225.5 美元）并且增加了工作时间（即在 132 周中增加了 667 个小时）。当埃塞俄比亚防止不良疗效的价值低于 19,000 美元且南非防止不良疗效的价值低于 14,500 美元时，短期治疗具有费用效益的可能性大于 95%。

结论 短期 MDR 治疗方案与卫生系统费用的大幅度降低以及参与者的经济负担减少有关。

Résumé

Évaluation économique d'un traitement de courte durée contre la tuberculose multirésistante en Éthiopie et en Afrique du Sud: l'essai STREAM

Objectif Étudier les variations de coût liées à l'adoption d'un traitement court de la tuberculose multirésistante (MR) pour les systèmes de santé et les participants.

Méthodes Nous avons comparé les coûts pris en charge par les systèmes de santé et les participants pour des schémas thérapeutiques longs (20 à 22 mois) et courts (9 à 11 mois) en Éthiopie et en Afrique du Sud. Les données ont été récoltées auprès des participants à la phase III de l'essai clinique randomisé STREAM, et nous avons estimé les dépenses assumées par les systèmes de santé en utilisant des approches ascendantes et descendantes. Enfin, pour analyser l'efficacité des coûts, nous avons calculé les frais additionnels qu'entraîne chaque issue défavorable évitée.

Résultats Les dépenses en soins de santé par participant en Afrique du Sud s'élevaient à 8340,7 dollars américains (US$) avec le traitement long et à 6618,0 US$ avec le traitement court; en Éthiopie, le montant équivalait respectivement à 6096,6 US$ et 4552,3 US$. La principale composante économique en Afrique du Sud était le coût des médicaments (67%, 1157,0 US$ sur un total de 1722,8 US$) tandis qu'en Éthiopie, il s'agissait de l'aide sociale (35%, 545,2 US$, sur un total de 1544,3 US$). En Éthiopie, les participants à l'essai clinique pour le traitement court ont signalé une baisse des dépenses consacrées à l'alimentation complémentaire (réduction moyenne par participant : 225,5 US$) et une hausse des heures de travail (c'est-à-dire 667 heures en plus sur 132 semaines). La probabilité que le traitement court soit plus rentable dépassait les 95% lorsque la valeur accordée aux issues défavorables évitées était inférieure à 19 000 US$ en Éthiopie, et à 14 500 US$ en Afrique du Sud.

Conclusion Le traitement court de la tuberculose MR a entraîné une importante diminution des dépenses pour les systèmes de santé, ainsi qu'une moindre charge financière pour les participants.

Резюме

Экономическая оценка краткосрочного курса лечения туберкулеза со множественной лекарственной устойчивостью(МЛУ-ТБ): исследование STREAM в Эфиопии и Южной Африке

Цель Изучение изменений в расходах для систем здравоохранения и участников в результате перехода на краткосрочную схему лечения туберкулеза со множественной лекарственной устойчивостью (МЛУ-ТБ).

Методы Авторы сравнили затраты систем здравоохранения и участников долгосрочных (от 20 до 22 месяцев) и краткосрочных (от 9 до 11 месяцев) схем лечения МЛУ-ТБ в Эфиопии и Южной Африке. Данные о затратах были получены от участников рандомизированного контролируемого клинического исследования фазы III STREAM. Авторы оценивали затраты системы здравоохранения, используя подходы «снизу вверх» и «сверху вниз». Оценка клинико-экономической эффективности выполнялась путем расчета дополнительных затрат на неблагоприятный исход, которого удалось избежать.

Результаты Расходы системы здравоохранения на одного участника в Южной Африке составляли 8340,7 долл. США для долгосрочной и 6618,0 долл. США для краткосрочной схемы лечения; в Эфиопии они составляли 6096,6 долл. США и 4552,3 долл. США соответственно. Самым крупным компонентом экономии были расходы на лекарственные препараты в Южной Африке (67%, 1157,0 долл. США от общей суммы 1722,8 долл. США) и расходы на социальную поддержку в Эфиопии (35%, 545,2 долл. США от общей суммы 1544,3 долл. США). В Эфиопии участники исследования по краткосрочной схеме лечения сообщали о более низких расходах на дополнительное питание (среднее сокращение на участника: 225,5 долл. США) и увеличении количества рабочих часов (то есть 667 дополнительных часов на протяжении 132 недель). Вероятность того, что краткосрочная схема лечения была более экономически рентабельной, превышала 95%, в то время как расходы на предотвращение неблагоприятного исхода в Эфиопии составили менее 19 000 долл. США, а в Южной Африке — менее 14 500 долл. США.

Вывод Краткосрочная схема лечения МЛУ-ТБ была связана со значительным сокращением расходов для системы здравоохранения и более низким финансовым бременем для участников.

Resumen

Evaluación económica del tratamiento a corto plazo de la tuberculosis multirresistente, Etiopía y Sudáfrica: el ensayo STREAM

Objetivo Investigar los cambios en los costos para los sistemas sanitarios y los participantes, derivados del cambio a planes de tratamiento a corto plazo para la tuberculosis multirresistente (MDR, por sus siglas en inglés).

Métodos Se compararon los costos para los sistemas sanitarios y los participantes de los planes de tratamiento a largo (20 a 22 meses) y a corto plazo (9 a 11 meses) de la tuberculosis en Etiopía y Sudáfrica. Se recopilaron datos sobre los costos de los participantes en el ensayo

STREAM fase III, controlado y aleatorizado y se estimaron los costos del sistema sanitario utilizando enfoques ascendentes y descendentes. Se realizó un análisis costo-efectividad calculando el costo incremental por cada resultado negativo que se evitó.

Resultados Los costos de atención sanitaria por participante en Sudáfrica fueron de 8340,7 dólares estadounidenses (USD) con el plan largo y de 6618,0 USD con el plan corto; en Etiopía, fueron de 6096,6 y 4552,3 USD, respectivamente. El mayor factor de ahorro fue el costo de los medicamentos en Sudáfrica (67 %; 1157,0 USD del total de 1722,8 USD) y los costos de apoyo social en Etiopía (35 %; 545,2 USD del total de 1544,3 USD). En Etiopía, los participantes del ensayo que siguieron el plan corto notificaron un menor gasto en alimentos suplementarios (reducción media por participante: 225,5 USD) y un aumento en las horas de trabajo (es decir, 667 horas adicionales en 132 semanas). La probabilidad de que el plan corto fuera rentable era superior al 95 % cuando el valor asignado para evitar un resultado negativo era inferior a 19 000 USD en Etiopía y a 14 500 USD en Sudáfrica.

Conclusión El plan de tratamiento a corto plazo de la tuberculosis MDR se asoció con una reducción sustancial de los costos del sistema sanitario y con una menor carga financiera para los participantes.

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Supplementary Appendix

1 CONTENTS

2 LIST OF ABBREVIATIONS

AHRI- Armauer Hansen Research Institute

CHEERS- Consolidated Health Economic Evaluation Reporting Standards

CRF- Clinical Report Form

GF- Global Fund

GHC- Global Health Committee

MDR-TB- Multidrug resistant tuberculosis

MoH- Ministry of Health

STREAM- The Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB

TB- Tuberculosis

3 LISTING OF SUPPLEMENTARY TABLES AND FIGURES

4 STREAM STUDY TEAM AND ADDITIONAL ACKNOWLEDGEMENTS

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5 BACKGROUND

Prior to the trial, there was evidence that Multi-Drug Resistant Tuberculosis (MDR-TB) patients in Ethiopia incurred out-of-pocket costs of up to $1,378 per MDR-TB episode.[1] The diagnosis of MDR-TB was shown to also affect employment status, household income, and ownership of assets.[1] Studies from South Africa found that the mean health system cost per MDR-TB patient is $17,164, forty times more than the cost of drug-susceptible Tuberculosis[2]. This estimate assumed a mean inpatient stay of 105 days, which revised treatment protocols have reduced considerably, although the costs of MDR-TB treatment still greatly exceed those involved in treating drug-susceptible TB. A number of shorter MDR-TB regimens are now being tested and implemented, so the need for an economic evaluation within the clinical trial was evident and the STREAM study is the first clinical trial of MDR-TB therapy to incorporate such an analysis undertaken.

Supplementary details of the methods and results presented elsewhere,[3] are reported below.

6 DETAILED METHODS

All costs were estimated in local currency and inflated to December 2017 prices using standard CPI indexes.[4] All costs are reported in 2017 USD, assuming exchange rates of 27.5 BIRR and 12.37 RAND to 1USD.[5]

Capital costs extending beyond 1 year (e.g. equipment) were annualised over their expected lifespan assuming a discount rate of 3%.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist has been used as a guide to optimise the preparation and reporting of the manuscript (Table 9).[6]

Separate costings were performed from a health system and from a patient perspective. Both costings adopted a trial-based perspective reflecting actual resources used, and costs borne by each participant as far as possible, excluding costs that were assessed solely related to research. This approach meant that the cost consequences of patient death are included in the analysis of the data.

6.1 HEALTH SYSTEM COSTING

The aim of the health system costing exercise was to estimate the health care resources required, in each participating country, to deliver the treatment specified in each arm of the clinical study. A local health economist for each country, with guidance from the UK-based health economists and the clinical lead for the health economic study, reviewed on-site documentation and national TB guidelines,[7,8] and consulted the

principal investigator at each of the four sites, to identify the expectations for tests, examinations, treatment, duration and frequency of inpatient and outpatient episodes during the entire treatment phase for each intervention, and information on any support payments offered. Information was obtained on the cadre of staff involved in delivering each aspect of care, the time required to deliver this care, and the tests, equipment and consumables required to deliver it.

The source of data on medication received by each participant was the clinical report forms (CRFs) of the clinical study. The different dosage adjustments or treatment interruptions were also considered in the costing exercise.

The time to smear conversion, which was used as a proxy for the inpatient stay, was sourced from the clinical study CRFs. The calculated inpatient stay durations can be seen in Table 1.

The information thus collected was used to develop a health system costing template for each country in Microsoft Excel. The costing template was also populated with unit cost information from a range of sources.

The unit prices used in the analysis for both Ethiopia and South Africa, together with their sources can be seen in Table 2 and Table 3. Where such information was not held or not available on-site, information was taken from the STREAM study budget.

For both countries, outpatient resource usage costs (laboratory test costs, specialist consultations costs and consumables costs) were calculated by multiplying unit costs by the quantity of resources used, determined by the clinical staff in accordance with the guidelines in each country.

The number of visits to health facility for the short regimen have been taken from the STREAM protocol- there were 12 visits in total, 7 during the intensive phase and 5 during the continuation phase. For the long regimen, the number of health facility visits were according to the national protocols in both countries.

The unit cost of staff time was based on the midpoint for the pay range of the relevant grade or cadre of staff. For AHRI and St Peter's, overhead costs such as building space and utilities were estimated from facility financial records. For South Africa, it was not possible to access such records so equivalent data were sourced from published literature.[9,10,11,12] Unit cost information, adjusted pro-rata, was combined with resource use data to estimate the total health system cost for each intervention, broken down by treatment phase.

The staff time by visit has been reported not to differ by regimen in South Africa. In Ethiopia, it has been reported that only the treatment initiation took longer (with approximate 150 minutes) for the short regimen compared to the long.

Patients in Ethiopia receive, while on out-patient treatment, a monthly social support payment of $36.34. This is funded through health sector budgets and was found to be a significant cost driver (30% of total cost under standard of care). There was zero cost associated with social support in South Africa, not because participants there did not receive any support payments, but because no such payments were made from health system budgets.

6.2 PARTICIPANT COSTS ESTIMATION

The questionnaire adapted after the STOP-TB patient cost questionnaire[13] asked participants to report direct costs (food, transport, medical fees) and indirect costs for both themselves and any supporters who assisted them during care-seeking. These costs related to routine visits made during the interval since the previous date of completion of the questionnaire. It also included questions to elicit information on coping strategies, such as loans taken out or assets disposed of.

The additional questionnaire was administered at randomisation to gather information on the pre-disease socioeconomic characteristics of participants, such as employment, income, hours worked, assets owned, and housing. At every 24 weeks subsequently, an adapted version of this questionnaire was administered to identify any changes in socioeconomic status or financial well-being.

These questionnaires were pilot-tested on MDR-TB patients that were not part of the STREAM trial before the health economic data collection commenced in each country. As a result of this, some of the questions were amended to improve clarity and provide additional answer options specific to certain contexts.

Training was provided for main trial staff in the administration of the health economic questionnaires by the local health economist. A quality assurance exercise was carried out during the data collection period in which a sample of questionnaires were reviewed by the local health economist, with support from the senior health economist, to assess the logic and credibility of responses. Feedback was provided to data collection staff on any issues raised from the exercise, so that they could improve their guidance to participants during data collection.

The responses to the participant cost questionnaire were not directly aggregated to estimate the total direct costs to participants of obtaining care. This is because participants within the study had to travel to health facilities to provide data for research, as well as to obtain care, so a crude summation of reported direct costs would not reflect the costs patients would face in a routine setting. To allow for this, data from participant cost questionnaires were used instead to estimate the unit direct cost to participants of a visit to a health facility. This was multiplied, for each arm, by the expected number of times a patient would need to visit the facility during usual clinical management (as advised by site PIs), to predict the costs that patients would incur in routine practice (conditional on survival and adherence to follow-up). Incremental indirect costs were calculated by estimating the total hours worked in each arm, over the duration of the study, using the area under the curve method, and reported as the difference in hours worked between arms. To adjust for missing data in the participant cost analysis, missing values were imputed using predictive mean matching, chained multiple imputation as the reference case.[14] Two responses were imputed under the missing at random assumption – expenditure of nutritional supplements and hours worked. Ten multiple imputed data sets with five iterations were generated. Variables included in both imputation models were age at trial enrolment, sex, weight, notable events and HIV status. Additionally, insurance and use of coping mechanism (borrowing or selling assets) were included when imputing missing values for expenditure on supplements, and variables denoting socioeconomic status were used when imputing missing values for hours worked (possession of a radio, main occupation, current employment). All analysis of participant cost data was performed in Stata v.15.1. (Stat Corp., USA).

For Ethiopia there were six deaths, four in the Short regimen and two in the Long regimen. Four of the patients died before any patient cost data could be collected (week 12) and therefore were not included in the patient costing data analysis. For the other two patients (one who died at week 18 and before the last follow-up visit respectively), the supplementary expenditure and number of working hours were adjusted to 0 at the next data collection points after their death.

Also, chained imputations could not be performed in South Africa due to the lack of data in both the imputed values as well as in the variables included in the imputation model. Due to the insufficient data, we could not estimate supplementary food expenditure or hours worked by participants in South Africa.

6.3 SERIOUS ADVERSE EVENTS COSTING

A further exercise was carried out in Ethiopia to estimate the costs associated with the diagnosis and management of serious adverse events (SAEs) (see Table 7). All SAEs except one were also grade 3 or higher adverse events under the Division of AIDS classification. [15]

We have included the costs for SAEs which were identified as being caused by MDR-TB or its treatment. SAEs judged to be treatment-related by the site PI were indicated on the form, while those categorised as TB-related have been identified by the clinical expert by analysing the SAE recording form. The clinical trial protocol exempted the reporting of SAEs caused by relapse or disease progression, therefore SAE costs related to these have not been included in our analysis. By excluding these costs, it is likely to have underestimated the SAE costs. However, this would apply for both arms of the trial so we would not expect significant SAE cost differences between the arms.

A serious adverse event costing tool was developed in Microsoft Excel to assist with the recording of data on all the healthcare resources used as a consequence of a serious adverse event. To populate the tool, the local health economist based in Ethiopia collected data from patient clinical records and interviews with staff involved in patient care, and included all tests, examinations, in-patient stays, outpatient visits, and medications received. These data were combined in the tool with unit costs obtained as described above, to calculate the total cost of care for that serious adverse event, from a health system perspective (see Table 7). This was then added to the total health system costs.

In the cost of monitoring ototoxicity, we have not included the cost of the hearing device the patient was provided with.

7 SUPPLEMENTARY RESULTS

7.1 PARTICIPANT CHARACTERISTICS

Table 4 gives details of the participants enrolled in the four sites participating in the STREAM economic evaluation.

7.2 PARTICIPANT COST ESTIMATION

The number of hours worked by participants in Ethiopia across the whole duration of the trial can be seen in Figure 1.

The mean spend on supplements decreased progressively throughout the course of treatment, from $77.91 (95% CI US$59.11- 96.72) to $1.86 (95% CI US$0.09- 3.62) per 3-months in the Short-regimen and from $118.91 (95% CI US$81.09- 156.73) to $4.07 (95% CI US$0.66-7.48) per 3-months in the Long-regimen (Figure 2).

7.3 SENSITIVITY ANALYSIS

Missing data from participants were imputed using multiple chain multiple imputation analysis. To test the robustness of the participant costs results, several sensitivity analyses have been performed. The results of these can be seen in Table 5 for the working hours analysis and in Table 6 for the costs of supplementary food.

To test the applicability of the results in the different hospital settings in South Africa, sensitivity analysis was carried out to explore how health system costs would vary if other inpatient stay unit costs reported in the literature were applied (Table 8). The Short regimen provides potential cost savings in all scenarios.

8 SUPPLEMENTARY TABLES

Table 1: Inpatient stay durations

Regimen/Site	Ethiopia	South Africa
Long regimen¬	9.64 weeks	9.02 weeks
Short regimen¬	9.62 weeks	9.43 weeks

¬Inpatient stay durations were not directly collected in the trial, for neither Long nor Short regimens. These were instead calculated using time to sputum smear conversion as a proxy (as explained in text)

Table 2: Unit costs and the sources used for the Health System Costing analysis in Ethiopia

Drug type/ Type of test	Estimated unit cost (US$, 2017) per tablet/vial	Source
Capreomycin 1gram powder for inj	4.75	Ministry of Health (MoH), Global Fund (GF) scale up plan for PMDT, 2011-2015
Cycloserine 250mg cap	0.49	
Ethambutol HCl 400mg	0.2	
Ethionamide 250mg	0.06	
Kanamycin 1g/4ml inj	2.44	
Levofloxacin 250mg	0.04	
Moxifloxacin 400 mg	0.49	
PAS acid sachet eq. to 4g aminosalicylic acid	1.26	
Isoniazid 300mg	2.34	
Pyrazinamide 400mg	0.02	
Protionamide 250mg	0.16	
Clofazimine 100mg	0.88	St. Peter's Pharmacy, Study Drugs Purchase Price List, 2016
AFB Stain/Smear	1.35	1) Hema Diagnostic Laboratory, St. Peter's Hospital, 2013. 2) Global Health Committee (GHC), 2013
Gram's Stain	1.5	
Sputum Culture	31.4	
Potassium	2.74	
Calcium	2.49	
Magnesium	2.44	
FSH	10.97	
TSH	6.23	
T4	6.28	
T3	6.28	
Creatinine	1.74	
SGOT/ALT	1.2	
SGPT/AST	1.2	
Uric acid	1.4	
Urine Analysis (Macro)/Urinalysis	1.5	
Urine Analysis (Chemical)	1.5	
Viral load	35.14	
HbA1c	1.45	
Full blood count	4.49	
HIV test	4.14	
HCG	1.99	
Stool (direct)	1.5	
Stool (concentrated)	2.49	
ECG	9.97	
CXR	12.11	STREAM 1 Budget, 2016

Surgical mask	0.21	St. Peter's Pharmacy, Study Drugs Purchase Price List, 2016
Particulate mask	2.45	
N-95 mask	2.24	
Surgical gloves, medium	0.19	
Examination gloves (7.5)	0.03	
Hospitalization costs per day	2.32	STREAM Trial Project Officer, AHRI, 2014
Hospitalization meal	6.69	MoH, GF scale up plan for PMDT, 2011-2015
Transportation (social support costs)/month	2.95	GHC STREAM budget, 2016 Interview with Finance Officer
Nutrition/food support (social support costs)/ month	13.75	
Housing rent (social support costs)/ month	19.65	
Inpatient Doctor per 10 minutes, per day	0.83	AHRI & St. Peter Human Resource for Government Salary Scale, 2013
Inpatient Nurse per consultation, per 15 minutes, per day	1.14	
Inpatient Psychiatrist, per 5 minutes, per day	0.11	
Staff costs (casher, accountant, cleaner, etc) per patient/month	3.09	Monthly Recurrent Expenditure, St. Peter's, 2012
Uniforms, clothing and bedding per patient/month	19.08	
Office supplies per patient/month	9.93	
Printing per patient/month	6.96	
Education supplies per patient/month	0.45	
Fuel and Lubricants per patient/month	22.57	
Other materials and supplies per patient/month	19.54	
Miscellaneous equipment per patient/month	0.9	
Research and Development supplies per patient/month	1.39	
Per Diem per patient/month	0.56	
Transport Fees per patient/month	0.49	
Official entertainment per patient/month	1.78	
Maintenance and repair of Plant, Machinery and Equipment per patient/month	7.36	
Rent per patient/month	2.17	
Advertising per patient/month	1.81	
Insurance per patient/month	3.32	
Freight per patient/month	3.16	
Fees and Charges per patient/month	2.71	
Electricity charges per patient/month	13.54	
Telecommunication charges per patient/month	5.74	
Water and Other utilities per patient/month	3.69	
Local Training per patient/month	9.03	

Table 3: Unit costs and the sources used for the Health System Costing analysis in South Africa

Drug type/ Type of test	Estimated unit cost (US$, 2017) per tablet/vial	Source
Kanamycin 1g vial	1.39	National Department of Health Master Procurement Catalogue, 2017
Isoniazid 300 mg tablet	0.05	
Protionamide 250mg tablet	0.09	
Moxifloxacin 400mg tablet	0.46	
Pyrazinamide 500mg tablet	0.03	
Clofazimine 100mg capsule	0.12	
Ethambutol 400mg tablet	0.05	
Moxifloxacin 400mg tablet	0.46	
Ethionamide 250mg	0.10	
Terizidone 250mg	0.75	
Amikacin	0.04	
Ethionamide	0.14	
Para-Aminosalicylic Acid	2.48	Pharmacist Sizwe Tropical Diseases Hospital Pharmacy Services, 2014
Imipenem High-dose	0.04	
Panadol 500mg	0.01	National Department of Health Master Procurement Catalogue, 2014
Ibuprofen 200mg	0.01	
Pyridoxine 25mg	0.00	
Maxolon	0.01	
Bactroban 3g Ointment	1.83	
Augmentin 250mg	0.02	
Augmentin 500mg	0.03	
Bactrim	0.01	
Codeine Phosphate	0.25	
Allergex	0.00	
Sunscreen	2.26	
Cough mixture	2.21	
Aquoeous cream	0.52	
Aspartate (amino)transaminase / AST	4.12	National Health Laboratory Service, 2014
Alanine (amino)transferase/ ALT	4.12	
Bilirubin total	3.20	
Bilirubin direct	2.43	
Phosphatase Alkaline	3.92	
(Gamma) Glutamyl transpeptidase	4.12	
Urine dipstick	1.16	
Fluid urea	2.75	
Urine sodium	2.75	
Urine potassium	2.75	

Urine creatine	2.75	
Creatinine	2.75	
Full blood count	5.26	
PCR for TB	55.64	
GeneXpert PCR TB	17.39	
TB PCR (Hain test)	17.66	
Full metabolic profile	255.11	
TSH receptor Ab	14.19	
Latex test for pregnancy	3.05	
ECG	8.88	Healthman Cardiology Costing Guide, 2016
Alcohol swab per piece	0.02	Tygerberg Hospital, Purchasing Records, 2014
Glove - disposable, non-sterile, latex per piece	0.02	
Mask - N95 per piece	0.12	
Mask per piece	0.03	RTC - S.Bruce, 2013
Hand sanitizer per piece	0.01	Rightmed Pharmacy- Y. Kilian, 2014
Medical Officer per minute	1.71	Occupation Specific Dispensation, Department of Public Service and Administration, 2014
Staff nurse per minute	0.41	
Counsellor per minute	0.09	
Room equipment per visit	7.65	Sizwe Tropical Diseases Hospital, 2014
Inpatient stay cost per day	67.89	Pooran et al[9]

Table 4: Participants characteristics

Centre/Characteristics			Age			Weight		
	Prop HIV+	No. of participants	25th centile	75th centile	Median	25th centile	75th centile	Median
AHRI	18%	71	26.48	35.33	29.66	44	54	48
St. Peter's	15%	55	28.05	35.15	31.56	45	56	52
Doris Goodwin	71%	61	28.33	52.51	33.21	48.98	56.95	51.15
Sizwe	82%	14	37.21	52.94	45.82	48.5	63.5	56

Table 5: Sensitivity analysis results showing the proportion of participants working full time (8 hours or longer) in Ethiopia

Sensitivity analysis/ assumptions made	Statistical significance of the difference in working hours between arms	Percentage of participants working 8 hours or longer at week 48
All missing values were replaced with the lowest number of hours worked during the trial	The difference between arms in number of hours worked is statistically significant at weeks 48 and 72; not statistically significant at weeks 24, 96, 120, 132	18% of participants in the Long regimen, compared to the 47% in the Short regimen

All missing values were left blank (complete case)	The difference between arms in number of hours worked is statistically significant at weeks 24, 48 and 72; not statistically significant at weeks 96, 120, 132	16% of participants in the Long Regimen, compared to 49% in the Short regimen
All missing values were replaced with 0	The difference between arms in number of hours worked is statistically significant at weeks 24, 48 and 72; not statistically significant at weeks 96, 120, 132	10% of participants in the Long regimen, compared to 38% in the Short regimen
All missing values were replaced with the sample mean	The difference between arms in number of hours worked is statistically significant at weeks 24, 48 and 72; not statistically significant at weeks 96, 120, 132	10% of participants in the Long regimen, compared to 38% in the Short regimen
Base case- chained multiple imputation	The difference between arms in number of hours worked is statistically significant at weeks 24, 48 and 72; not statistically significant at weeks 96, 120, 132	30% of participants in the Long regimen, compared to 52% in the Short regimen

Table 6: Sensitivity analyses results showing the cumulative difference in supplementary food purchase between Long and Short regimen in Ethiopia.

Sensitivity analysis/Assumptions made	Results- cumulative difference in supplementary food purchase between Long and Short regimen
All missing data has been replaced with the maximum reported amount spent during the trial (or with 0 if this was the single cost reported)	The cumulative difference in spending between the Long regimen and Short regimen is of US$204 (US$708 vs. US$535)
All missing data were left blank (Complete Case)	The cumulative difference in spending between the Long regimen and Short regimen is of US$182 (US$499 vs. US$317)
All missing data were replaced with the sample mean	The cumulative difference in spending between the Long regimen and Short regimen is of US$112 (US$449 vs. US$337)

Base case- Chained Multiple Imputations	The cumulative difference in spending between the Long regimen and Short regimen is of US$216 (US$549 vs. US$333)

Table 7: Serious adverse event costing split by the main cost drivers and by treatment regimen

System Organ Class	Serious adverse event	Number of serious adverse events costed	Cost drivers					Unit cost per serious adverse event ($)	No. long regimen	No. short regimen	Long regimen costs ($)	Short regimen costs ($)
			Drug costs ($)	Test costs ($)	Staff cost ($)	Hospitalization costs ($)	Consultation costs ($)					
Psychiatric disorders	Acute psychosis	1	10.86	2.23	2.72	90.65	2.41	108.87	3	4	326.61	435.48
	Depression	1	4.04	6.40	63.22	7.25	2.41	83.32	2	0	166.64	0.00
	Anxiety	1	38.02	16.80	3.03	32.64	2.41	92.89	1	0	92.89	0.00
Metabolism and nutrition disorders	Hypokalaemia	1	127.44	28.91	8.13	90.65	2.41	257.55	7	1	1802.84	257.55
	Tetany	1	3.62	17.54	6.06	83.40	2.41	113.03	5	1	565.14	113.03
Hepatobiliary disorders	Fulminant hepatitis	1	7.17	78.14	9.63	0.00	2.41	97.34	0	1	0.00	97.34
	Drug induced hepatitis	1	0.00	48.17	8.79	284.23	2.41	343.60	0	1	0.00	343.60
Gastrointestinal disorders	Gastritis	1	28.57	2.23	69.13	18.13	2.41	120.46	1	0	120.46	0.00
	Vomiting	1	6.66	11.48	15.16	0.00	2.41	35.70	1	0	35.70	0.00
	Dyspepsia	1	14.95	31.55	11.68	19.41	2.41	80.00	1	0	80.00	0.00
General disorders and administration site conditions	Death	1	0.00	15.78	5.84	3.51	2.41	27.53	0	1	0.00	27.53
Cardiac disorders	Palpitation	1	74.34	35.54	63.43	0.00	2.41	175.71	1	0	175.71	0.00
Ear and labyrinth disorders	Ototoxicity	1	31.02	6.40	20.67	0.00	2.41	60.51	0	1	0.00	60.51
	Total							**1596.52**	22	10	3366.00	1226.17
	Total per participant										**82.10**	**15.71**

Figure 1: Number of hours worked per day by participants in Ethiopia

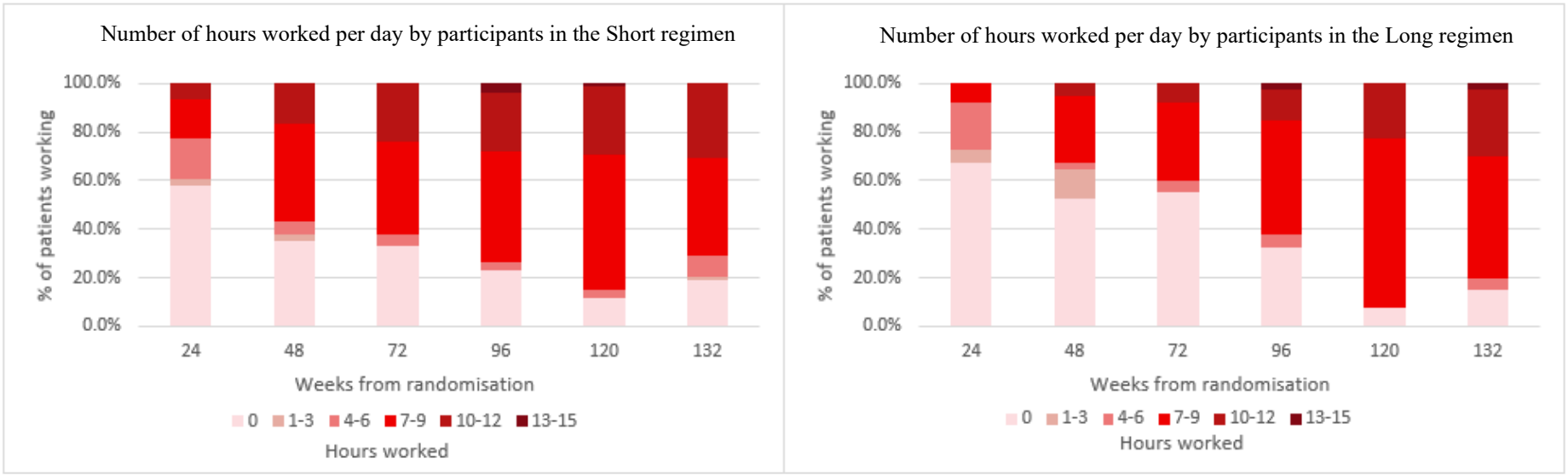
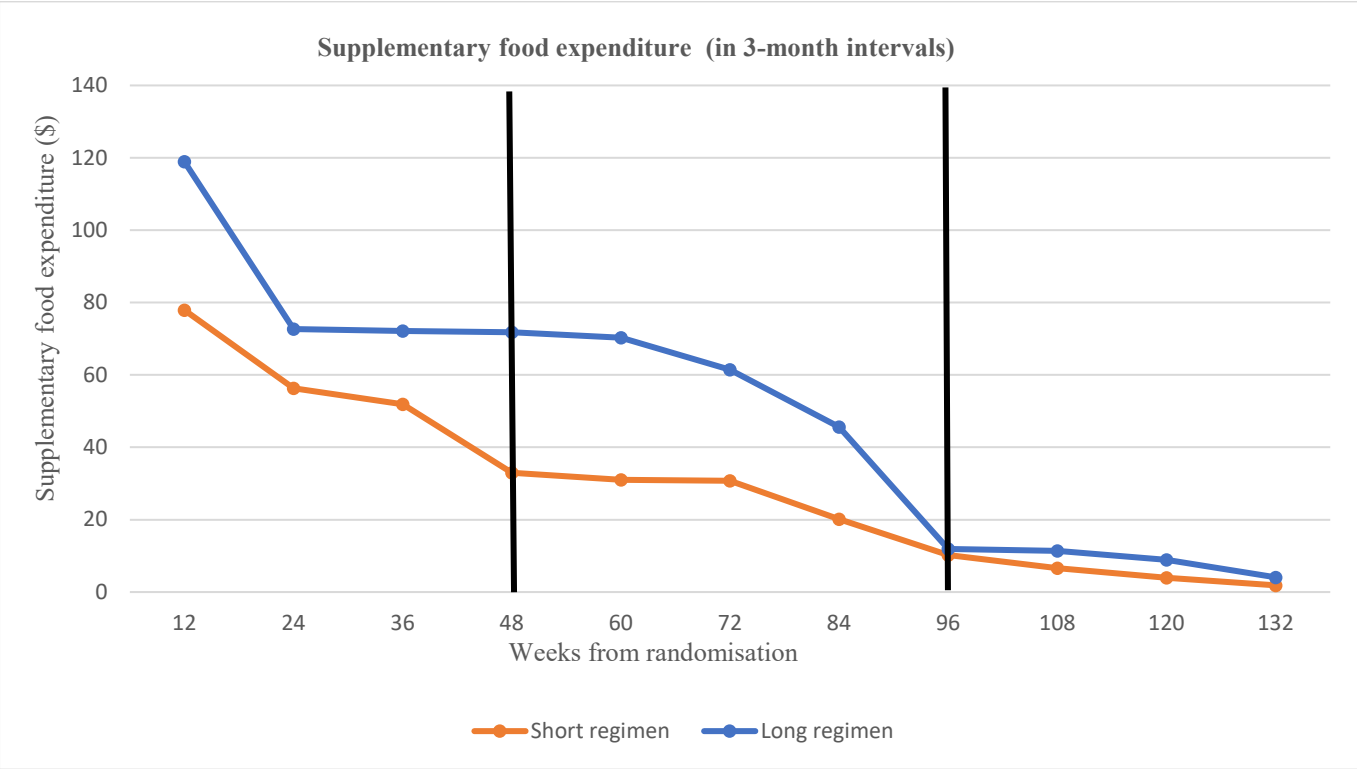


Figure 2: Supplementary food expenditure in Short and Long regimens in Ethiopia



The vertical lines represent the nearest data collection point after treatment completion in the two regimens. Treatment completion in the Short regimen, is around 40 weeks, but the nearest data collection point after this is at week 48, where the difference deepens. The Long regimen completion is around 86 weeks, but the nearest data collection point after this is at 96 weeks, where the difference in supplementary food spending between regimens becomes negligible

Table 8: Health system costs univariate deterministic sensitivity analysis using estimates for the different care models for inpatient stay costs

Regimen	Health system costing/ inpatient costs estimations	Cox et al[10]	Base case-Pooran et al[9]	Sinanovic et al[11]	Sinanovic et al[11]	Loveday et al[12]	Schnippel et al[2]	Loveday et al[12]	Loveday et al[12]
		$47.1	$67.9	$75.3	$103.9	$184.9	$187.7	$194.9	$234.9
Short	Inpatient costs estimations	$5,248.1	$6,620.0	$7,111.5	$8,997.2	$14,342.9	$14,524.9	$15,004.4	$17,641.2
Long		$7,028.8	$8,340.8	$8,810.8	$10,614.1	$15,726.2	$15,900.3	$16,358.8	$18,880.4
Incremental cost Long vs. Short		$1,780.7	$1,720.7	$1,699.3	$1,616.9	$1,383.3	$1,375.4	$1,354.4	$1,239.2

*All costs were updated to 2017 prices. Cost per day

Table 9: Consolidated Health Economic Reporting Standard checklist

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title is STREAM: An economic evaluation of a short standardised regimen for the treatment of rifampicin-resistant TB
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	At start of paper
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for	Covered in Background section

		health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	Page 7 of the Supplement
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Opening paragraph of Methods
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Opening paragraph of Methods
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Opening paragraph of Methods
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Analysis section of Methods
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5 of the Supplement
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	The 'unfavourable outcome' used was a composite outcome: unfavourable bacteriologic outcome (7 participants in the Long and 26 in the Short regimen), death (5 participants in the Long and 9 in the Short regimen), treatment extension or change after adverse event (3 participants in the Long and 4 in the Short regimen), start more than two additional drug therapies (3 participants in the Long and 2 in the Short regimen), not seen at 76 weeks (4 participants in the Long and 8 in the Short regimen), treatment extension or change after poor adherence or loss to follow-up (3 participants in the Long and 3 in the Short regimen)
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Reference to the clinical paper
	11b	*Synthesis-based estimates*: Describe fully the methods used for	N/A

		identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Fully described in Methods section and in the supplement
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	In supplement, section 6, Table 2 and Table 3
Choice of model	15	Describe and give reasons for the	N/A as not a model-based evaluation

		specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A as not a model-based evaluation
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Analysis section of Methods and supplement section 6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	See text on participant cost results and health system cost results (in the manuscript) and supplementary table on unit costs (Table 1 and Table 2 in the supplement)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-	Bar graphs, plus text in Results section and Abstract

		effectiveness ratios.	

Characterizing uncertainty	**20a**	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Results section of the manuscript. Sensitivity analyses are reported in the supplement.
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Ethiopia and South Africa are reported separately
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	In the discussion section of the manuscript
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Acknowledgements
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Acknowledgements

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BMJ Open

Economic evaluation protocol of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial

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ABSTRACT

Introduction A December 2019 WHO rapid communication recommended the use of 9-month all-oral regimens for treating multidrug-resistant tuberculosis (MDR-TB). Besides the clinical benefits, they are thought to be less costly than the injectable-containing regimens, for both the patient and the health system. STREAM is the first randomised controlled trial with an economical evaluation to compare all-oral and injectable-containing 9–11-month MDR-TB treatment regimens.

Methods and analysis Health system costs of delivering a 9-month injectable-containing regimen and a 9-month all-oral bedaquiline-containing regimen will be collected in Ethiopia, India, Moldova and Uganda, using 'bottom-up' and 'top-down' costing approaches. Patient costs will be collected using questionnaires that have been developed based on the STOP-TB questionnaire. The primary objective of the study is to estimate the cost utility of the two regimens, from a health system perspective. Secondary objectives include estimating the cost utility from a societal perspective as well as evaluating the cost-effectiveness of the regimens, using both health system and societal perspectives. The effect measure for the cost–utility analysis will be the quality-adjusted life years (QALY), while the effect measure for the cost-effectiveness analysis will be the efficacy outcome from the clinical trial.

Ethics and dissemination The study has been evaluated and approved by the Ethics Advisory Group of the *International Union Against Tuberculosis and Lung Disease* and also approved by ethics committees in all participating countries. All participants have provided written informed consent. The results of the economic evaluation will be published in a peer-reviewed journal.

Trial registration number ISRCTN18148631.

Strengths and limitations of this study

- The economic evaluation of STREAM will be the first study to estimate the costs incurred by both patients undergoing multidrug-resistant tuberculosis treatment and the healthcare system within a phase III randomised controlled trial.
- The detailed costing and analysis in four different settings will provide valuable insights into the timings and drivers of the costs associated with implementation of a 9-month all-oral bedaquiline-containing regimen. The study will generate important evidence needed for future policy decisions and the shaping of targeted interventions.
- The trial setting means that additional research costs (e.g. costs for collecting pharmacokinetic samples, social support costs paid for by the study) that would not be incurred in a routine setting will be incurred. These research costs will be separated out and eliminated from the costing analysis. Additionally, the experience of participants and delivery of health services (e.g. frequency of visits) will in places, inevitably deviate from routine practice, with implications for patient and health system costs. Though we will attempt to adjust for these differences in analysis, guaranteeing no interference may not be possible.

BACKGROUND

The STREAM trial is a phase III non-inferiority randomised controlled trial (RCT) to test the efficacy, safety and economical impact of shortened multidrug-resistant tuberculosis (MDR-TB) treatment regimens. MDR-TB is a form of tuberculosis (TB) caused by bacteria that cannot be treated with two of the most powerful, first-line anti-TB drugs, isoniazid and rifampicin. Globally, in 2017, there were a little over half a million people with TB resistant to rifampicin, and out of these, 82% had MDR-TB.[1]

The WHO's End TB Strategy is among the health targets of the Sustainable Development Goals. It was adopted by the World Health Assembly in 2014 with the aim of reducing TB deaths by 90% and new cases by 80% between 2015 and 2030, as well as reducing to zero the number of households incurring catastrophic costs due to TB by 2020. Currently, global TB incidence is falling at 2% per year, which is

insufficient to reach the 2020 milestone.[2] This means that new ways of addressing the disease must be found to meet these targets. Careful evaluation of alternative treatment strategies is vital to ensure the most effective and feasible approaches are implemented.

The December 2019 WHO rapid communication recommends the use of shorter, all-oral, bedaquiline-containing regimens for patients with MDR-TB.[3] It seems that all-oral regimens, as opposed to those containing injectables, are becoming the preferred option for treatment of MDR-TB as data from the South African TB programme had suggested them to improve patient outcomes. Replacing the injectable with bedaquiline resulted in better treatment success and better adherence.[3] Besides the clinical benefits, it is also thought that the all-oral treatment leads to lower costs from a health system and patient perspective.[4] It is therefore crucial to test these hypotheses via an RCT in multiple settings. Furthermore, to date, no phase III trial has included an economic analysis of the 9-month bedaquiline-containing regimen, making it difficult for policymakers to assess the economical and financial impact. STREAM is the first randomised phase III trial to include such an analysis, to compare the all-oral, bedaquiline-containing and injectable-containing 9–11-month MDR-TB treatment regimens.

Objectives

The questions that the economical evaluation is aiming to address include:

- What are the health system costs of treating patients with MDR-TB using the following regimens: a 9-month injectable regimen; a 9-month all-oral bedaquiline-containing regimen and a 6-month injectable regimen?
- What costs do patients face during and after treatment?
- How does MDR-TB affect patients' socioeconomic situations?
- What financial coping mechanisms do patients employ?

The primary economical objective is to estimate the cost utility of the two MDR-TB interventions, in each country, from a health system perspective. To achieve this, an economical evaluation of both the costs and consequences associated with each intervention will be conducted.

Secondary economical objectives include assessing the cost utility of the regimens from a societal perspective and evaluating the cost-effectiveness of the regimens from both a health system and societal perspective.

The effect measure for the cost–utility analysis will be the QALY, while the effect measure of the cost-effectiveness analysis will be the efficacy outcome from the clinical trial that is favourable or unfavourable.

METHODS AND ANALYSIS

Randomised controlled trial design

Health economics data will be collected alongside the STREAM trial. Its protocol has been published elsewhere.[5] In brief, the STREAM study is an international, multicentre, parallel-group RCT of patients with MDR-TB and patients with rifampicin-resistant and isoniazid-sensitive TB. It will be assessed whether the proportion of participants on regimen C with a favourable efficacy outcome at week 76 is not less on that on regimen B, that is, C is non-inferior to B. Data will also be collected on regimen D for secondary comparisons. Treatments administered are outlined in figure 1 and explained below. Trial recruitment started in April 2016, across 13 sites in 7 countries (table 1).

At the start of Stage 2, randomisation was to regimen A, regimen B, regimen C and regimen D, in a ratio of 1:2:2:2, done using a web-based system managed by Medical Research Council Clinical Trials Unit (MRC CTU). Version 8.0 of the protocol limits randomisation to arms B and C, so patients will no longer be randomised to regimen A and regimen D and randomisation will be in a ratio of 1:1. At least 200 patients to each of regimen B and regimen C will be randomised, across all sites. This was determined based on the assumption that the proportion of patients with a favourable efficacy outcome at week 76 is 80% for regimen B and 82% for regimen C. With a non-inferiority margin of 10% and a one-sided significance level of 2.5%, 180 evaluable patients will be required in each of the two regimens to demonstrate non-inferiority.

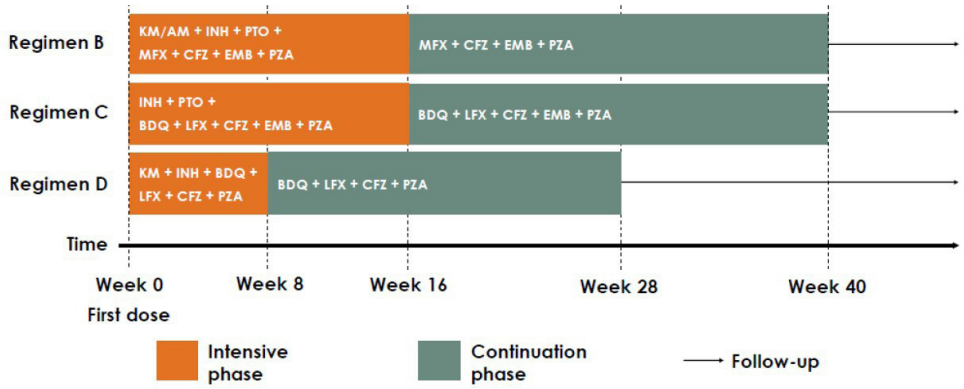

Figure 1 Treatments outline. Regimen A was dropped of the trial.

Table 1 STREAM trial sites

	Clinical trial sites	HE sites
Mongolia	National Center for Communicable Diseases, Ulaanbaatar	
Ethiopia	Armauer Hansen Research Institute, Addis Ababa	x
	St. Peter's Hospital, Addis Ababa	x
South Africa	King Dinuzulu Hospital, Durban	
	Helen Joseph Hospital, Johannesburg	
	Empilweni TB Hospital, Port Elizabeth	
	Doris Goodwin, Pietermaritzburg	
Moldova	IMSP, Chiril Draganiuc, Chisinau	x
Uganda	Mulago Hospital, Kampala	x
Georgia	National Center for Tuberculosis and Lung Disease, Tbilisi	
India	B.J. Medical College, Ahmedabad	x
	National Institute for Research in Tuberculosis, Chennai	x
	Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, Delhi	x

If 10% of patients will be excluded from the primary efficacy analysis population, a total of 400 patients would be required in total for regimens B and C[5].

The health economic analysis will include participants of the clinical trial in the above-mentioned sites, who are over 18 years old and fulfil the inclusion/exclusion criteria as outlined in the trial protocol. All patients in the study will be followed up until week 132, with the primary analysis conducted on data collected up to week 76.

Patient data will be collected at 12-week intervals, during the patient assessment visits for the clinical trial, using a questionnaire developed based on the STOP-TB questionnaire, in all health economic sites.

Health system cost data will be collected by the focal health economists in each country during the whole trial period.

The Consolidated Health Economic Evaluation Reporting Standards checklist has been used as a guide to optimise the preparation and reporting of the methods used (online supplemental annex 1).

Health system resource use and costs

A mixture of top-down and bottom-up approaches will be used.

Data regarding staff time and staff activities involved in the management of MDR-TB treatment for each regimen will be collected by the focal health economists in each country using a standardised questionnaire developed by the health economic team, pilot tested in all HE sites and used in the first phase of the trial.[6]

A full assessment of the health system costs of delivering the MDR-TB regimens, including tests performed, consumables used, inpatient stay costs, drugs administered and overheads, will be done in each country, for each arm. Any relevant resource events will also be included. These will be collected by the focal health economists in each country using hospitals' accounting records, clinical trial casa report forms (CRFs) and STREAM protocol, and will be costed using local unit costs where possible. Where this will not be possible, STREAM or in-country private healthcare facilities unit costs will be used.

The costs associated with the diagnosis and management of serious adverse events caused by MDR-TB or its treatment will also be included. The costing will include all tests performed, examinations, investigations, inpatient stays and medication received, as well as staff costs. Data will be collected in an event costing tool developed in Microsoft Excel by the HE trial team and the main data source will be the clinical trial CRFs.

The total health system costs for each trial arm will be estimated by summing the costs of each resource used and presented by the following cost elements, by phase (see table 2).

Capital costs extending beyond 1 year (eg, equipment) will be annualised over their expected lifespan assuming a discount rate of 3%.

Research costs such as costs related to the pharmacokinetics study will not be collected or included in this economic evaluation. The health system costing will be done in close collaboration with the central health economic team to make sure it is sensible and evaluated with the support of a team of clinicians involved in the clinical trial. If deemed appropriate, other research costs that do not reflect usual practice will be excluded.

Patient costs

Patient costs will be collected by administering questionnaires that have been developed based on the STOP-TB questionnaire.[7] Data will be collected in two stages. First, a baseline questionnaire will capture socioeconomic data of each patient before they start treatment. Then, a follow-up questionnaire capturing any changes to the socioeconomic data and a patient treatment cost questionnaire will be administered every 12 weeks.

The patient costs to be collected are presented in table 3.

The total direct cost per participant receiving MDR-TB treatment will be calculated as follows:

$$\text{Total direct cost} = (\text{CostDots} * \text{NoVisitsD}) + (\text{CostSVisits} * \text{NoVisitsS}) + (\text{CostUVisit} * \text{NoVisitsU}) + \text{CostSupp}$$

where NoVisitsD, NoVisitsS, NoVisitsU=number of visits for attending DOTs, scheduled and unscheduled visits, respectively.

Usually, patients with TB are accompanied by a guardian to the direct observed treatment (DOT) and/or assessment visits. The guardians' direct costs (transport, food and accommodation costs) for each patient and for each visit will be included in the patient–costs analysis. Patients

Table 2 Health system costs sources and calculation methods

Cost element	Unit	Data sources: Costs sources	Data sources: Quantity used per treatment phase (intensive, continuation and follow-up until week 76)	Method
Inpatient stay	Cost per day	Local hospitals' accounting records or local private facilities if not available	Actual number of inpatient stay days for all patients	Unit cost per day multiplied by the number of inpatient days for each patient
Laboratory tests	Cost per test	Local hospitals' laboratories or local private facilities if not available	Frequency from the STREAM trial protocol	Cost per test multiplied by the number of tests performed for each patient
Medication	Unit cost per tablet/dose	Local hospitals' pharmacies purchasing lists (alternative drug price lists if not available locally)	Dosages, treatment interruptions, etc, from the STREAM trial clinical CRFs	Unit cost per dose multiplied by the total number of doses for each patient
Staff	Cost per minute	Local pay scales	Time collected using staff questionnaire	Unit cost per minute multiplied by number of minutes in a visit multiplied by number of total visits
Social support	Cost per week	TB national programme	TB national programme	Cost per week times number of weeks the patient is eligible for social support
Consumables	Per patient per visit	Local hospitals' pharmacies purchasing lists or local private pharmacies	Quantity of each unit collected via direct observation and staff questionnaire	Unit cost per patient per visit multiplied by the number of visits.
Serious adverse events (SAEs)	Per patient per SAE	A combination of all the above	A combination of all the above	Unit costs of: consumables, lab tests, medication, staff will multiplied by the quantity of each to calculate the cost of managing each SAE
Overheads	Overhead costs per patient per day	As reported by the local hospitals accounting records	As reported by the local hospitals. Number of patients in the TB unit will be used as a proxy.	Total overhead costs will be calculated for the TB unit over a year, then divided by the number of patients with TB in a year

who indicate they had a 'guardian' during treatment will be asked whether this guardian lost an income when accompanying them; their lost time will be assumed to equal the patient's and valued at the national minimum wage.

All participants, conditional on survival to week 76, will be included in the primary analysis. In the secondary analysis, all modified intention to treat participants will be included, treating missing answers as missing data and handled as explained in the missing data section below.

All costs will be collected in the local currency and converted to US$ using the exchange rate reported by OANDA[8] at the time of the analysis. All costs will be inflated to 2021 prices.

Due to logistics issues, data collection for the health economic component was delayed at two Indian sites, Ahmedabad and Chennai, and the Ugandan site, so baseline and week 12 patient data will be collected at the week 24 or week 36 visit for the first patients enrolled into the trial. This will be subject to sensitivity analysis. All interviews after week 36 will be conducted as scheduled, during the patient assessment visits.

The analysis will be performed in Stata (Stata, USA) and for each cost category, descriptive statistics (mean, median, SE and IQR) will be presented.

Quality assurance exercises will be carried out regularly during data collection by the central Health Economics team, to assess the logic and credibility of responses. Feedback will be provided to data collection staff on any issues raised from the exercise, so that they could correct and improve their guidance to participants during data collection.

Health-realted Quality ofLife measurement

For the primary outcome calculations, patient health states will be measured prospectively using the EQ-5D-5L[9] every 12weeks from week 0 (i.e. baseline), before the patient takes the first drug, until week 76. The responses

Table 3 Patient cost data collection method and analysis plan

Cost type	Data collection method	Analysis
Cost of attending direct observed treatment (DOTs) (CostDots)	Through patient CRFs (transport and food costs data)	For each cost type category, data will be aggregated for each site and arm, to estimate the mean direct cost per visit
Costs of attending injection DOTs (CostDots)	Through patient CRFs (transport and food costs data)	
Patient cost for attending scheduled patient assessment visits (CostSVisits)	Through patient CRFs (transport and food costs data)	
Patient costs for attending unscheduled patient assessment visits (CostUVisits)	Through patient CRFs (transport and food costs data)	
Food supplements (CostSupp)	Through patient CRFs	Mean spend for each time point to be calculated and presented as the cumulative difference in food purchases between arms
Income loss during and after treatment	Reported by patients if willing to reveal their income at each time point; if not, working hours reported to be used as a proxy	If patients are unwilling to reveal their income, average salary values from the specific areas in each country will be used. The total lost hours will be multiplied with the hourly average wage. Total income loss during treatment and follow-up will be calculated

to the questionnaire will be converted into health utility scores using the most appropriate tariff for each country, selected based on geographical proximity and economical context. Currently, the tariffs that we propose to use are from Indonesia (for India), Ethiopia (for Ethiopia and Uganda) and Poland (for Moldova) and can be seen in online supplemental annex 2. We will use updated value sets if these become available before the analysis stage. The value sets will be used to calculate the HRQoL for each patient at each interview point. Observations for each patient will be combined to calculate a QALY score for each arm using the 'area under the curve' linear method, using the formula below:

$$\text{QALY} = \sum \left[\frac{(U_i + U_{i+1})}{2} \right] \times (t_{i+1} - t_i)$$

where U=utility value and t=time between interviews.

QALY calculations will also account for mortality during the follow-up period, by assigning 0 QALYs from time of death until the end of follow-up.

The health system costs will be calculated on a per patient basis and together with the QALY outcome will be used to calculate the incremental cost-effectiveness ratio (ICER) of regimen C to regimen B, using the formula below:

$$\text{ICER} = \frac{(\text{Cost}_{\text{RegimenC}} - \text{Cost}_{\text{RegimenB}})}{(\text{Mean QALY}_{\text{RegimenC}} - \text{Mean QALY}_{\text{RegimenB}})}$$

Cost-effectiveness acceptability curves will be constructed to compare the regimens' probabilities of being cost-effective against a set of pre-set threshold values, ranging from US$0 to US$100 000 and including some published estimates.[10]

Secondary objectives

Secondary objectives will consider the primary clinical outcome in the clinical trial. This is a favourable outcome, where a participant had their last two culture results, taken on separate visits but no more than 6 weeks earlier than week 76, negative or an unfavourable outcome.

For the societal perspective analyses, direct patient costs data collected as explained above will be added to the health system costs to calculate the societal costs.

Subgroup analyses

We will present data disaggregated by age, sex, HIV status, site and other variables may be presented where they will be identified in the study as potentially relevant.

Missing data

The nature and pattern of missing data will be analysed. If necessary, multiple imputation techniques[11] will be used to address the missing data in the base case, by using relevant baseline variables. This method is recommended for economical evaluations alongside clinical trials.[12] Other methods such as complete case analysis, average imputation, lowest and highest point imputation and listwise deletion will be tested in the sensitivity analysis.

Statistical analysis

We will present our results in terms of precision, that is, how close the data are expected to be to the true population value, presenting means and SD of the results. 95% CI ranges will be constructed and presented such that there is a 95% probability that the results will contain the true population parameter.[13]

Sensitivity analyses

Sensitivity analyses will be used to test the robustness of the results. Planned sensitivity analyses can be seen in table 4 ; however, any other things that become important will also be tested.

A non-parametric bootstrapping approach will be used to determine the level of sampling uncertainty

Table 4 Planned sensitivity analyses

Parameters	Rationale/method
Complete-case analysis, Average imputation, lowest and highest point imputation	If the level of missing observations for costs and HRQoL is higher than 10%, the MI technique is more prone to bias. Data sets will be analysed to assess whether the results indicate similar conclusions
Patient data collected retrospectively in India and Uganda	As some data have been collected retrospectively during the trial due to logistics issues, two data sets, one including the retrospectively collected data (where recall bias might have occurred) and one excluding it, will be analysed to assess whether the results indicate similar conclusions.
On the most important cost drivers	Unit costs will vary across different sites in the same country. Therefore, deterministic sensitivity analysis will be conducted to assess whether the results change as unit costs of the most important cost drivers are varied within plausible ranges.
Parameter uncertainty	Probabilistic sensitivity analysis to explore uncertainties surrounding key parameters; 1000 simulations will be run, and results presented as mean costs and QALYs.
Inpatient stay	Since 2011, WHO recommends outpatient models of care for patients with multidrug-resistant tuberculosis. The analysis will be re-run excluding inpatient stay costs

surrounding the mean ICER by generating 1000 estimates of incremental costs and outcomes. These will be presented on a cost-effectiveness plane. CIs of the generated ICERs will then be calculated, in order to summarise the uncertainty due to sampling variations.

Net monetary benefit (NMB) will be calculated for each bootstrap estimate for a range of cost-effectiveness thresholds as follows:

$$\mathrm{NMB} = (\lambda * \mathrm{QALYs}) - \mathrm{Costs}$$

where λ represents the cost-effectiveness threshold. This will be calculated as one to three times Gross Domestic Product (GDP) per capita, and other thresholds from country guidance or the literature. The regimen with NMB>0 or with the highest NMB should be adopted. Mean NMB will be reported with 95% bootstrap CIs and z-test conducted.

Patient and public involvement

WHO's End TB Strategy includes policy goals around elimination of patient catastrophic costs, and this study has been developed to measure and inform both public and stakeholders regarding the economical impact of MDR-TB on patients.

The health economic research questions were developed based on the STOP-TB questionnaire by the health economic team involved in conducting the study at Liverpool School of Tropical Medicine and University of Warwick, based on clinical practice, trial protocol and literature review. All health economic questionnaires have been pilot tested with opportunity for patients to give feedback.

Community advisory boards (CABs), comprised of volunteers from (among others) community-based organisations, those affected by TB and sometimes trial team members, are functioning with the support of the trial at all 13 STREAM Stage 2 sites. Most CABs were formed at site initiation and, therefore, did not inform the development of the research question and outcome measures; however, input on the trial protocol was received from the Global TB CAB. The STREAM CABs act as coordinating mechanisms for community engagement at STREAM trial sites. Their activities include community outreach (engaging the local communities and key populations to raise awareness and literacy on MDR-TB, research, and the trial), provision of psychosocial support to study patients and advocacy activities aimed at improving programmes and policies. The CABs also meet regularly with their respective study teams for trial updates and to pass on patient and community feedback from the trial. Results of the trial will be disseminated to participants and affected communities, with the support of STREAM CABs, likely at outreach events for participants and their families.

The burden of the intervention will be assessed by the patients taking part in the health economic component of the trial, through the EQ-5D-5L questionnaire, which is a self-reported measure of quality of life. These patients will also assess the economic impact the disease had, by reporting changes in income and employment status throughout the study.

COVID-19 impact

Also, the COVID-19 outbreak started during the trial. Lockdown has been imposed on 18th March in Uganda and on 24th March in India, while Moldova and Ethiopia declared state of emergency in March 2020. It is expected that the COVID-19 mitigating measures taken in most countries will affect the socioeconomic status of the patients and their quality of life, independent of their MDR-TB or MDR-TB treatment.[14] There are a few measures that will be taken to record this. A COVID-19 diary, containing information about the lockdown

restrictions, will be completed by each site (see online supplemental annex 3). Also, an additional questionnaire has been developed to further explore some of the answers regarding their income, spending and health-related quality of life.

As data collection started in 2016, before the outbreak, the lockdown imposed will be modelled as an independent explanatory variable for parameters such as quality of life, working hours and supplements spending during intensive, continuation and post-treatment phase. If the variable turns out to be significant, we will use it to adjust values reported post pandemic, using model predictions of what would have been reported if the pandemic hadn't happened.

Additional changes to the protocol as a result of COVID-19 may be implemented as needed.

DISCUSSION

STREAM will be the first study to estimate the costs incurred by both patients undergoing MDR-TB treatment and the healthcare system within a phase III RCT.

The detailed costing and analysis in four different settings will provide insights into the timing and drivers of the cost saving or dissaving of implementing a 9-month all-oral bedaquiline-containing regimen, providing the data for targeted interventions if needed.

The study will have certain limitations. The EQ-5D-5L is not a condition-specific measure, and so may miss differences in symptoms that are important to participants. Also, our method assumes a linear relationship between values at different time points; however, this might not be accurate. It was considered not feasible to ask participants to complete the EQ-5D-5L questionnaire at a more frequent interval, that is, each DOT visit.

The trial setting also means that the experience of participants might be different from routine practice, in ways that could influence costs, such as the frequency of visits and their location and the provision of support (eg, transport vouchers, food vouchers).

Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

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Collaborators STREAM Study Health Economic Evaluation Collaborators: Mamo Girma, Vanita Patel, Makwana Mukesh, Malaisamy Muniyandi, Shravan Kumar, Sangeetha Subramani, Saleem Ahmad, Jasper Nidoi, Irina Pirlog, Mariana Macarie, I.D. Rusen, Gay Bronson, Meera Gurumurthy, Karen Sanders, Sarah Meredith, Andrew Nunn, Ben Spittle, Wendy Dodds, Robyn Henry-Cockles, Rachel Bennett, Elisa Giallongo, Danni Maas, Rachel Bennett, Ruth Goodall, Saiam Ahmed, Claire Cook, Katharine Bellenger, Gopalan Narendran, Bruce Kirenga, Elena Tudor, Rajesh Solanki, Daniel Meressa, Adamu Bayissa, Anuj Bhatnagar, STREAM community advisory boards (CABs).

Contributors SBS has obtained research funding, is the principal investigator of the study and contributed to the original design of this economic study. LR drafted the protocol and contributed to the design of this study. JM, EW and ET provided helpful feedback for all aspects of the work, contributed to the design of the study and revised the draft manuscript.

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-Supplementary material-

Annex 1- CHEERS Checklist

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title is: Economic evaluation of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	N/A as it is an analysis plan
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Covered in Background and Objectives sections
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	Covered in the Methods and Analysis section
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Covered in the Methods and Analysis section
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Covered in the Methods and Analysis section
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Covered in the Methods and Analysis section
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Covered in the Methods and Analysis section
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	In the Methods section, Health system resource use and cost sub-heading
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Covered in the Methods and Analysis section
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Reference to the clinical paper; Covered in the Methods and Analysis section
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A

Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Fully described in Methods and Analysis section
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Dates of the estimated resource quantities and unit costs not reported as this is a protocol. Methods for adjusting the unit costs and converting costs into a common currency are covered in the Methods and Analysis section, after the Patient costs sub-heading.
Choice of model	15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	N/A as not a model-based evaluation
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A as not a model-based evaluation
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Fully covered in the Methods and Analysis section, in the Missing data, Statistical analysis and Sensitivity analyses sub-sections.
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A as this is a study protocol, but these will be presented in the main paper as stated in this protocol
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	N/A as this is a study protocol, but these will be presented in the main paper as stated in this protocol

Characterizing uncertainty	**20a**	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Methods and Analysis section of the protocol-Sensitivity analyses sub-heading.
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Costs and outcomes will be presented separately for each country

Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Discussion about the strengths and limitations in the Discussion section; the key findings and their generalizability will be presented in the paper.
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Acknowledgements
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Acknowledgements

Annex 2- Value sets to be used

Independent variables of the model	C-TTO Tobit model censored at −1			DCE conditional logistic model rescaled			Hybrid model censored C-TTO values at −1 (final value set)		
	Coeff.	(SE)	*p* value	Coeff.	(SE)	*p* value	Coeff.	(SE)	*p* value
Mobility (MO)									
No problems to slight problems	0.088	(0.015)	0.000	0.139	(0.015)	0.000	0.119	(0.008)	0.000
Slight problems to moderate problems	0.086	(0.017)	0.000	0.080	(0.017)	0.000	0.073	(0.011)	0.000
Moderate problems to severe problems	0.250	(0.019)	0.000	0.196	(0.016)	0.000	0.218	(0.013)	0.000
Severe problems to unable	0.170	(0.018)	0.000	0.219	(0.018)	0.000	0.203	(0.012)	0.000
Self-care (SC)									
No problems to slight problems	0.085	(0.014)	0.000	0.101	(0.016)	0.000	0.101	(0.007)	0.000
Slight problems to moderate problems	0.056	(0.018)	0.002	0.038	(0.018)	0.032	0.039	(0.010)	0.000
Moderate problems to severe problems	0.128	(0.018)	0.000	0.085	(0.019)	0.000	0.108	(0.013)	0.000
Severe problems to unable	0.035	(0.016)	0.030	0.097	(0.017)	0.000	0.068	(0.012)	0.000
Usual activities (UA)									
No problems to slight problems	0.071	(0.015)	0.000	0.092	(0.016)	0.000	0.090	(0.006)	0.000
Slight problems to moderate problems	0.106	(0.017)	0.000	0.051	(0.017)	0.003	0.066	(0.011)	0.000
Moderate problems to severe problems	0.137	(0.019)	0.000	0.154	(0.017)	0.000	0.145	(0.013)	0.000
Severe problems to unable	0.061	(0.018)	0.001	0.091	(0.017)	0.000	0.084	(0.013)	0.000
Pain/discomfort (PD)									
No problems to slight problems	0.089	(0.013)	0.000	0.081	(0.016)	0.000	0.086	(0.006)	0.000
Slight problems to moderate problems	0.007	(0.019)	0.721	0.012	(0.018)	0.513	0.009	(0.011)	0.395
Moderate problems to severe problems	0.135	(0.018)	0.000	0.085	(0.017)	0.000	0.103	(0.013)	0.000
Severe problems to extreme problems	0.024	(0.019)	0.211	0.053	(0.018)	0.003	0.048	(0.013)	0.000
Anxiety/depression (AD)									
No problems to slight problems	0.079	(0.014)	0.000	0.050	(0.017)	0.003	0.079	(0.006)	0.000
Slight problems to moderate problems	0.055	(0.018)	0.002	0.061	(0.017)	0.000	0.055	(0.011)	0.000
Moderate problems to severe problems	0.086	(0.017)	0.000	0.114	(0.018)	0.000	0.093	(0.012)	0.000
Severe problems to extreme problems	0.062	(0.016)	0.000	0.085	(0.018)	0.000	0.078	(0.012)	0.000
Log likelihood	−6189.97			−3958.62			−9325.84		
AIC	12,421.93			7957.24			18,735.69		
BIC	12,572.19			8109.23			19,060.41		
Examples of estimated utility values									
U(21111)	0.912			0.861			0.881		
U(31111)	0.826			0.781			0.808		
U(41111)	0.576			0.585			0.590		
U(51111)	0.406			0.366			0.387		
U(12345)	0.225			0.268			0.240		
U(21231)	0.745			0.676			0.696		
U(55555)	−0.810			−0.884			−0.865		

AIC Akaike information criteria, *BIC* Bayesian information criteria, *C-TTO* composite time trade-off, *DCE* discrete choice experiments, SE standard error

Table 1- Value set to be used for India. Purba FD, Hunfeld JAM, Iskandarsyah A, et al. The Indonesian EQ-5D-5L Value Set. Pharmacoeconomics. 2017;35(11):1153-1165. doi:10.1007/s40273-017-0538-9

Independent variables of the model	C-TTO OLS model			DCE conditional logistic model rescaled			Hybrid model censored C-TTO values at -1 (final value set)		
	Coef.	(SE)	p-value	Coef.	(SE)	p-value	Coef.	(SE)	p-value
Mobility (MO)									
MO2	0.0047	0.014	0.729	0.4780	0.061	0.000	0.0337	0.005	0.000
MO3	0.0166	0.015	0.262	0.1138	0.071	0.110	0.0307	0.009	0.000
MO4	0.1748	0.016	0.000	0.9810	0.070	0.000	0.1632	0.010	0.000
MO5	0.1038	0.016	0.000	0.7434	0.074	0.000	0.1322	0.010	0.000
Self-care (SC)									
SC2	0.0036	0.013	0.785	0.2044	0.067	0.002	0.0235	0.005	0.000
SC3	0.0494	0.016	0.002	-0.0024	0.074	0.974	0.0160	0.008	0.042
SC4	0.1189	0.015	0.000	0.6849	0.078	0.000	0.1024	0.009	0.000
SC5	0.0826	0.013	0.000	0.4234	0.073	0.000	0.0804	0.009	0.000
Usual-activities (UA)									
UA2	0.0188	0.014	0.176	0.3470	0.063	0.000	0.0323	0.005	0.000
UA3	0.0441	0.014	0.002	-0.0391	0.071	0.579	0.0160	0.008	0.042
UA4	0.1299	0.016	0.000	0.5818	0.071	0.000	0.1091	0.009	0.000
UA5	0.0936	0.015	0.000	0.6079	0.076	0.000	0.1147	0.010	0.000
Pain/discomfort (PD)									
PD2	0.0140	0.013	0.266	0.4499	0.067	0.000	0.0361	0.004	0.000
PD3	0.0161	0.017	0.331	0.1090	0.073	0.136	0.0155	0.008	0.061
PD4	0.2452	0.015	0.000	1.1358	0.077	0.000	0.2187	0.010	0.000
PD5	0.1421	0.016	0.000	0.5689	0.076	0.000	0.1361	0.011	0.000
Anxiety/depression (AD)									
AD2	0.0111	0.014	0.428	0.2718	0.070	0.000	0.0259	0.004	0.000
AD3	0.0381	0.015	0.012	0.3516	0.072	0.000	0.0589	0.008	0.000
AD4	0.2322	0.015	0.000	1.1803	0.079	0.000	0.2139	0.009	0.000
AD5	0.1414	0.013	0.000	0.8320	0.078	0.000	0.1591	0.010	0.000
AIC	10587.06			6498.30			14002.09		
BIC	10739.33			6650.17			14336.81		
Order of importance									
	AD			AD			AD		
	PD			MO			PD		
	MO			PD			MO		
	UA			UA			UA		
	SC			SC			SC		

Coef. – coefficient; SE – standard error

Items with a negative coefficient (in grey) represent inconsistent items
Order of importance based on sum of disutility which is the disutility associated with level 5

Table 2- Value set to be used for Uganda and Ethiopia. Welie AG, Gebretekle GB, Stolk E, Mukuria C, Krahn MD, Enquoselassie F, Fenta TG. Valuing health state: an EQ-5D-5L value set for Ethiopians. Value Health Reg Issues. 2019;22:7–14

	Model 1 panel, random effects	Model 2 Bayesian	Model 3 M2 + random parameters	Model 4 M3 + error scaling with *t*-Student	Model 5 M4 + religion scaling	Final model M5 + DCE, censoring
Const.	0.005 (−0.010; 0.019)	Not used	Not used	Not used	Not used	Not used
MO2	0.021 (0.002; 0.039)	0.023 (0.001; 0.044)	0.058 (0.013; 0.073)	0.017 (0.014; 0.022)	0.019 (0.014; 0.023)	0.025 (0.020; 0.029)
MO3	0.012 (−0.007; 0.031)	0.016 (0.000; 0.036)	0.077 (0.021; 0.094)	0.015 (0.005; 0.026)	0.016 (0.005; 0.028)	0.034 (0.026; 0.042)
MO4	0.098 (0.077; 0.118)	0.101 (0.074; 0.129)	0.159 (0.071; 0.181)	0.101 (0.085; 0.116)	0.107 (0.090; 0.124)	0.126 (0.113; 0.141)
MO5	**0.262 (0.238; 0.285)**	**0.263 (0.239; 0.289)**	**0.303 (0.271; 0.330)**	**0.251 (0.228; 0.274)**	**0.267 (0.242; 0.293)**	**0.314 (0.286; 0.342)**
SC2	0.030 (0.014; 0.046)	0.037 (0.015; 0.059)	0.015 (0.003; 0.087)	0.029 (0.024; 0.034)	0.031 (0.026; 0.036)	0.031 (0.027; 0.036)
SC3	0.038 (0.017; 0.059)	0.042 (0.014; 0.071)	0.005 (0.000; 0.119)	0.037 (0.028; 0.047)	0.040 (0.029; 0.050)	0.047 (0.040; 0.055)
SC4	0.122 (0.098; 0.146)	0.116 (0.089; 0.143)	0.042 (0.027; 0.180)	0.108 (0.094; 0.123)	0.115 (0.099; 0.131)	0.111 (0.099; 0.123)
SC5	**0.276 (0.254; 0.298)**	**0.269 (0.244; 0.295)**	**0.242 (0.193; 0.268)**	**0.258 (0.237; 0.282)**	**0.273 (0.249; 0.299)**	**0.264 (0.243; 0.286)**
UA2	0.031 (0.014; 0.048)	0.034 (0.011; 0.058)	0.002 (0.000; 0.007)	0.033 (0.026; 0.039)	0.034 (0.028; 0.042)	0.023 (0.019; 0.027)
UA3	0.032 (0.009; 0.054)	0.041 (0.015; 0.067)	0.005 (0.000; 0.014)	0.050 (0.040; 0.060)	0.053 (0.043; 0.063)	0.040 (0.032; 0.048)
UA4	0.092 (0.070; 0.115)	0.088 (0.062; 0.115)	0.024 (0.010; 0.038)	0.104 (0.091; 0.117)	0.110 (0.095; 0.125)	0.097 (0.087; 0.107)
UA5	**0.186 (0.167; 0.206)**	**0.183 (0.157; 0.209)**	**0.180 (0.161; 0.201)**	**0.180 (0.161; 0.200)**	**0.190 (0.169; 0.212)**	**0.205 (0.188; 0.224)**
PD2	0.028 (0.012; 0.044)	0.033 (0.012; 0.054)	0.041 (0.028; 0.054)	0.025 (0.021; 0.028)	0.026 (0.022; 0.030)	0.030 (0.026; 0.034)
PD3	0.034 (0.014; 0.053)	0.035 (0.007; 0.063)	0.053 (0.036; 0.071)	0.030 (0.022; 0.039)	0.032 (0.022; 0.041)	0.050 (0.043; 0.058)
PD4	0.229 (0.208; 0.251)	0.228 (0.204; 0.254)	0.253 (0.224; 0.276)	0.223 (0.208; 0.239)	0.235 (0.217; 0.253)	0.261 (0.244; 0.280)
PD5	**0.467 (0.440; 0.494)**	**0.473 (0.446; 0.499)**	**0.490 (0.464; 0.518)**	**0.492 (0.463; 0.520)**	**0.519 (0.485; 0.555)**	**0.575 (0.538; 0.613)**
AD2	0.024 (0.006; 0.041)	0.032 (0.010; 0.054)	0.049 (0.015; 0.061)	0.019 (0.016; 0.023)	0.020 (0.017; 0.024)	0.018 (0.015; 0.021)
AD3	0.034 (0.011; 0.056)	0.033 (0.006; 0.058)	0.085 (0.038; 0.101)	0.037 (0.026; 0.049)	0.039 (0.027; 0.052)	0.029 (0.022; 0.037)
AD4	0.114 (0.094; 0.135)	0.114 (0.088; 0.139)	0.160 (0.116; 0.181)	0.119 (0.106; 0.132)	0.126 (0.113; 0.142)	0.108 (0.097; 0.119)
AD5	**0.224 (0.203; 0.244)**	**0.226 (0.201; 0.251)**	**0.176 (0.153; 0.231)**	**0.211 (0.194; 0.229)**	**0.223 (0.204; 0.243)**	**0.232 (0.213; 0.252)**
Deviance	61.2% (R^2 used instead)	11,866	−777	−13,781	−13,780	−9215
DIC		11,886	2597	−9704	−9704	−9215[a]
PSRF	n.a.	All <1.01	Maximum = 15	All <1.01	All <1.01	All <1.01
Maximum *u* (not 11111)	0.983	0.984	0.998	0.985	0.984	0.982
u (22222)	0.862	0.841	0.834	0.877	0.870	0.873
u (33333)	0.847	0.833	0.775	0.830	0.821	0.800
u (44444)	0.340	0.352	0.361	0.345	0.307	0.296
u (55555)	− 0.420	− 0.415	− 0.391	− 0.392	− 0.471	− 0.590
% states $u < 0$	2.85	2.88	2.69	2.78	4.26	6.66
Dimension order	PD, SC, MO, AD, UA	PD, SC, MO, AD, UA	PD, MO, SC, UA, AD	PD, SC, MO, AD, UA	PD, SC, MO, AD, UA	PD, MO, SC, AD, UA
Levels consistency	MO3 < MO2	MO3 < MO2	SC3 < SC2	MO3 < MO2	MO3 < MO2	Consistent

AD anxiety/depression, *DCE* discrete choice experiment, *DIC* deviance information criterion, *M* model, *MO* mobility, *n.a.* *PD* pain/discomfort, *PSRF* potential scale reduction factor, *SC* self-care, *u* utility, *UA* usual activities

[a]Failed to calculate penalty in JAGS ("support of observed nodes is not fixed")

Table 3- Value set to be used for Moldova. Golicki, D., Jakubczyk, M., Graczyk, K. et al. Valuation of EQ-5D-5L Health States in Poland: the First EQ-VT-Based Study in Central and Eastern Europe. PharmacoEconomics 37, 1165–1176 (2019). https://doi.org/10.1007/s40273-019-00811-7

Annex 3- COVID19 diary

COVID19 diary

-to be completed by focal health economists at each site-

Epidemiology of the Epidemic

- First case notification date

Details of policies declared by central/federal/state government that potentially restrict "Normal" daily life. Date implemented/Details of policy/Date lifted

- Lockdown start date
- Specific restrictions- what's the rule of going outside the house? What's the rule for going out for work?
- Law enforcement- are people being fined for going out?

- Are entertainment places open (cinemas, theatres shopping centres)? Are cricket, football, etc. competitions still taking place? If not, when were these stopped?
- Lockdown end date

Impact on daily life (descriptive/opinion) behavioural picture

- Country's general perception regarding COVID19- are they scared, complaint with the rules, are they indifferent
- Can you find basic supplies in the markets/supermarkets? Rice, bread? Is there a price increase amongst basic supplies?
- Are people living with their families during the lockdown? Have they travelled to their home town/village during the lockdown?
- Any shortage in drug supplies?
- Anything else you would like to report, that would influence the patients' income and their quality of life?

Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial^

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Summary

Background The STREAM stage 2 trial assessed two bedaquiline-containing regimens for rifampicin-resistant tuberculosis: a 9-month all-oral regimen and a 6-month regimen containing an injectable drug for the first 2 months. We did a within-trial economic evaluation of these regimens.

Methods STREAM stage 2 was an international, phase 3, non-inferiority randomised trial in which participants with rifampicin-resistant tuberculosis were randomly assigned (1:2:2:2) to the 2011 WHO regimen (terminated early), a 9-month injectable-containing regimen (control regimen), a 9-month all-oral regimen with bedaquiline (oral regimen), or a 6-month regimen with bedaquiline and an injectable for the first 2 months (6-month regimen). We prospectively collected direct and indirect costs and health-related quality of life data from trial participants until week 76 of follow-up. Cost-effectiveness of the oral and 6-month regimens versus control was estimated in four countries (oral regimen) and two countries (6-month regimen), using health-related quality of life for cost-utility analysis and trial efficacy for cost-effectiveness analysis. This trial is registered with ISRCTN, ISRCTN18148631.

Findings 300 participants were included in the economic analyses (Ethiopia, 61; India, 142; Moldova, 51; Uganda, 46). In the cost-utility analysis, the oral regimen was not cost-effective in Ethiopia, India, Moldova, and Uganda from either a provider or societal perspective. In Moldova, the oral regimen was dominant from a societal perspective. In the cost-effectiveness analysis, the oral regimen was likely to be cost-effective from a provider perspective at willingness-to-pay thresholds per additional favourable outcome of more than US$4500 in Ethiopia, $1900 in India, $3950 in Moldova, and $7900 in Uganda, and from a societal perspective at thresholds of more than $15 900 in Ethiopia, $3150 in India, and $4350 in Uganda, while in Moldova the oral regimen was dominant. In Ethiopia and India, the 6-month regimen would cost tuberculosis programmes and participants less than the control regimen and was highly likely to be cost-effective in both cost-utility analysis and cost-effectiveness analysis. Reducing the bedaquiline price from $1·81 to $1·00 per tablet made the oral regimen cost-effective in the provider-perspective cost-utility analysis in India and Moldova and dominate over the control regimen in the provider-perspective cost-effectiveness analysis in India.

Interpretation At current costs, the oral bedaquiline-containing regimen for rifampicin-resistant tuberculosis is unlikely to be cost-effective in many low-income and middle-income countries. The 6-month regimen represents a cost-effective alternative if injectable use for 2 months is acceptable.

Funding USAID and Janssen Research & Development.

Introduction

Tuberculosis that is resistant to rifampicin, with or without resistance to other first-line antituberculosis drugs, continues to be a global public health threat. Current treatment for rifampicin-resistant tuberculosis requires a drug regimen lasting a minimum of 9 months, and up to 20 months, although this is expected to be reduced to 6 months in the forthcoming WHO guidelines.[1] Treatment of rifampicin-resistant tuberculosis costs patients and health providers more than treatment of drug-susceptible tuberculosis, and has a lower success rate (59% *vs* 86%).[2,3] The WHO clinical recommendations[1,4] do not include directly measured comparative economic data.

STREAM stage 2 is a multicountry randomised controlled trial assessing two new bedaquiline-containing treatment regimens for rifampicin-resistant

^Indicates that this paper version and the published version differ slightly due to thesis examiner clarification requests

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See Comment page e183

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See Online for appendix

Research in context

Evidence before this study

In 2020, WHO recommended a short, all-oral treatment regimen for rifampicin-resistant tuberculosis. However, the guidelines were published before availability of directly measured economic data comparing all-oral to existing treatment regimens, relying instead on modelling work, which indicated that an all-oral regimen had the possibility to achieve improved treatment outcomes and reduce lifelong disability, while also enabling patients to return to employment sooner than an injectable-containing regimen. In making their 2020 recommendation, the WHO Guideline Development Group rated the overall certainty of evidence "very low", and acknowledged that implementing the all-oral shorter regimen does not automatically and immediately eliminate or reduce costs. Several modelling studies using data from the first bedaquiline trial have suggested that an oral regimen would decrease costs and increase quality-adjusted life-years gained, but no study has directly collected efficacy outcomes, patient-reported costs, or quality of life data. Given the economic impact of rifampicin-resistant tuberculosis, the global policy goals of financial protection and elimination of catastrophic costs for patients with tuberculosis, and the resource constraints facing health providers in countries where rifampicin-resistant tuberculosis is a substantial challenge, there was a clear need for additional, robust evidence on the economics of shorter treatment regimens, to support health programmes considering these new strategies. We searched PubMed for within-trial economic evaluations published from Jan 1, 2016, to June 16, 2022, with the terms "trial" AND "tuberculosis" AND "rifampicin resistance" OR "rifampicin-resistance" OR "rifampin resistance" OR "rifampin-resistance" OR "MDR" OR "multidrug" OR "multi-drug" OR "MDR-TB" OR "RR-TB" AND "economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "QALY" OR "cost", with no language or article type restrictions. This search yielded 71 results; studies that were not randomised clinical trials were excluded, leaving just one study, the STREAM stage 1 economic evaluation, which did not compare bedaquiline-containing regimens.

Added value of this study

The STREAM stage 2 economic evaluation uses a within-trial and multicountry approach, offering detailed analyses and comparisons of the provider and participant costs, as well as participant quality of life data over the treatment duration and for 36 weeks (for the oral and control regimens) and 48 weeks (for the 6-month regimen) after treatment completion. The results show that a 9-month, oral, bedaquiline-containing regimen is unlikely to be either cost-saving or cost-effective compared with a 9-month regimen that includes daily injections for the first 4 months. Although the oral regimen had superior clinical outcomes, the participant-reported quality of life data were not significantly different across the two intervention groups. Moreover, participants in both groups had similar levels of catastrophic health-related costs. A 6-month, bedaquiline-based regimen is a cost-effective alternative if daily injections for 2 months are acceptable for patients, clinicians, and policy makers.

Implications of all the available evidence

Our findings provide robust evidence on the cost-utility and cost-effectiveness of two new rifampicin-resistant tuberculosis regimens. The data on likely costs, potential savings, and patient-reported outcomes can be used to guide uptake and implementation of regimens by national tuberculosis programmes. Results suggest that provider costs, including drug costs, will need to be reduced to enable cost-effective delivery of 9-month bedaquiline-based regimens; otherwise, providers will need to allocate additional resources for treating rifampicin-resistant tuberculosis. The results also provide crucial information for use in designing financial protection packages for patients.

tuberculosis versus a 9-month control previously evaluated in STREAM stage 1.[5] Both STREAM stage 1 and STREAM stage 2 included within-trial economic evaluations, to support global policy recommendations and decisions by tuberculosis programmes on the best rifampicin-resistant tuberculosis regimen for their health system and health financing context. The STREAM stage 2 economic study was done (with minor modifications, see appendix pp 11–12) in line with the health economic analysis plan published elsewhere.[6]

This study was done in Ethiopia, India, Moldova, and Uganda and presents the costs and cost-effectiveness associated with the oral, 6-month, and control regimens of STREAM stage 2. We present participant costs, catastrophic costs, and provider costs for each regimen and explore associated cost drivers. We separately compared the oral and 6-month regimens versus the control regimen in two economic evaluations, initially from the provider perspective and separately from the societal perspective. The primary economic evaluation is a cost-utility analysis using health-related quality of life data, collected from participants during the treatment duration and follow-up period, as the outcome. The secondary evaluation is a cost-effectiveness analysis using the efficacy outcome (favourable or unfavourable) from the clinical trial.[6]

Methods

Study design and participants

The clinical trial design has been described in detail elsewhere.[7] In brief, STREAM stage 2 was an international, multicentre, non-inferiority randomised controlled trial done in 13 hospital clinics in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda). The Union Ethics Advisory Group was the global ethics committee. Ethical approvals were also obtained

from national and institutional ethics committees of participating sites. At recruitment, participants aged 15 years or older (where approved, otherwise 18 years or older) with rifampicin-resistant tuberculosis without fluoroquinolone or aminoglycoside resistance were randomly assigned (1:2:2:2) by a web-based randomisation system to a 20-month injectable-containing regimen (WHO-recommended regimen from 2011 to 2018), a 9-month injectable-containing regimen (moxifloxacin, clofazimine, ethambutol, and pyrazinamide for 40 weeks, with kanamycin, high-dose isoniazid, and prothionamide given for the 16-week intensive phase; control regimen) recommended by WHO from 2016 when STREAM stage 2 began to 2020, a 9-month all-oral regimen with bedaquiline (identical to control, except that bedaquiline for 40 weeks replaced kanamycin and levofloxacin replaced moxifloxacin; oral regimen), or a 6-month regimen with bedaquiline and an injectable for the first 2 months (bedaquiline, clofazimine, pyrazinamide, and levofloxacin for 28 weeks, with high-dose isoniazid with kanamycin for an 8-week intensive phase; 6-month regimen). Randomisation to the 20-month and 6-month regimens ceased early at most sites.[7]

The primary trial objective was to determine whether the proportion of participants in the modified intention-to-treat population with a favourable efficacy outcome at week 76 in the oral regimen group was non-inferior to that in the control group. Assessment of the 6-month regimen versus control was a secondary objective. The modified intention-to-treat population was defined as all randomly assigned participants with a positive culture for *Mycobacterium tuberculosis* at screening or randomisation, apart from participants with isolates obtained before randomisation who were subsequently found to be susceptible to rifampicin or resistant to both fluoroquinolones and second-line injectable drugs on phenotypic drug-susceptibility testing. Treatment for rifampicin-resistant tuberculosis was administered free at the point of care for all patients (as it would be under programmatic conditions), in publicly funded health facilities.

Health economic data were collected from four of the seven countries in STREAM stage 2: Ethiopia, India, Moldova, and Uganda. All participants who fulfilled the inclusion criteria as outlined in the trial protocol,[7] were older than 18 years, provided written informed consent, and responded to the health economic questionnaires at least once were included in the health economic study.

The analyses presented here cover the period from randomisation until week 76 of follow-up. This time horizon captures 36 weeks (for the oral and control regimens) and 48 weeks (for the 6-month regimen) of data after completion of tuberculosis treatment. We contend that this time horizon is sufficiently long to capture any important between-group differences in treatment outcomes, survival, serious adverse events, and therefore health-related quality of life, that would be likely to have an effect beyond 76 weeks. Further details are provided in the appendix (p 10) and Discussion section.

Procedures

Participant costs were collected between June 20, 2016, and July 29, 2021, using an adapted STOP TB Partnership questionnaire, administered in the local language of each site during the scheduled trial follow-up visits.[8] Data on both medical spending (consultation fees, administration fees, and drugs) and non-medical spending (food and transport) were collected at baseline and then every 12 weeks until week 60 and finally at week 76. For further details see appendix (p 8).

We used bottom-up and top-down methods to collect provider costs.[9] Duration of hospital stay, medication use, and social support payments were collected for each participant; consumable costs were obtained from aggregate data using activity-based costing and allocated to individual participants using a suitable proxy. Site-specific tuberculosis care activities (eg, patient management processes), their timing, and resources used were determined from interviews with clinical and managerial staff at each site. Laboratory tests were assumed to follow the trial's assessment schedule for each regimen.[7] Individual participant care records for each serious adverse event were used to identify and cost the number and type of tests done, examination duration, and consumables used.

Health-related quality of life responses, used for the cost-utility analyses, were collected every 12 weeks from week 0 until week 60 and at week 76, using the EQ-5D-5L form translated into the local language at each site.[10] Participants were asked to rate their health on five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Missing responses were multiple imputed. If a participant died during follow-up, we assumed that their responses were 5 for each dimension (ie, worst possible health state) since their last interview until last follow-up visit at week 76.

The efficacy outcome used for cost-effectiveness analyses was the pooled (all seven trial countries) primary endpoint of favourable outcome at 76 weeks.[7] Favourable status was defined as a culture negative for *M tuberculosis* at week 76 and on the previous visit, with no intervening positive culture or previous unfavourable outcome. Unfavourable outcomes were the initiation of bedaquiline, kanamycin, linezolid, or two or more other drugs if they were not included in the assigned regimen; treatment extension beyond the permitted duration; death from any cause; a positive culture from one of the two most recent specimens; or no week 76 visit.

Cost data

Direct cost per participant was estimated by multiplying the cost of each directly observed treatment or assessment

visit by the number of visits. Guardian costs were assumed to equal the participant's non-medical direct costs and, for participants who indicated they required a guardian to accompany them during treatment, these were included in the total visit cost. Supplementary food expenditure (eg, on additional fruits, meat, and energy drinks) was reported separately.

Indirect costs were estimated using the output approach, by subtracting the self-reported (every 12 weeks) individual income from all sources, including social support, during tuberculosis treatment from the participants' self-reported pre-tuberculosis income, pro-rata for the 76 weeks of follow-up.[11] If participants reported that their guardian lost income, this was assumed to be equivalent to the participant's income loss.

Missing values in participants' responses for participant (and guardian) costs incurred for directly observed treatment and assessment visits (transport and food), lost income, and supplementary food expenditure were imputed using chained imputation models using a predictive mean matching algorithm.[12] All participant costs were estimated from treatment start until week 76 of follow-up or participants' last visit if they discontinued early or died. We considered total participant costs to be catastrophic if they exceeded 20% of annual individual income, approximating (for a combination of pragmatic reasons, see appendix p 8) to the WHO definition that uses household income.[13]

Inpatient hotel costs were calculated by dividing the total annual expenditure on hotel costs by the number of annual inpatient stay days, for each institution. Data were obtained from public hospital records where possible, with data from private hospitals or market prices used where hospital records were not available (see appendix p 7). To this cost, we added the staff costs. Outpatient visit costs were calculated by multiplying the quantity of each resource used as reported in clinical staff interviews (laboratory tests, staff time, consumables, etc) by their unit cost.

We used treatment logs to calculate medication intake for each participant. Total number of pills taken was multiplied by the Global Drug Facility unit cost (highest price available) for each drug to estimate regimen medication costs.[14] If a participant was transferred to a salvage regimen anytime during the 76-week follow-up period, total salvage regimen costs (ie, even if extending beyond 76 weeks) were included in the respective trial group costs.

Social support costs were calculated by multiplying the country-specific amount by the outpatient duration or treatment duration as per country norms. Research costs (eg, payments received for attending trial-related visits) were excluded from participant and provider costs.

Where serious adverse events were related to either rifampicin-resistant tuberculosis or its treatment (assessment made independently by two clinicians, see appendix p 7), serious adverse event management costs were included in the analysis. Each resource used (staff, tests, and consumables) was multiplied by its unit cost from hospital records and, when not available, from the local private facilities. We focused on serious adverse events rather than adverse events because many adverse events were minor and had relatively few cost implications, and because there was a practical limit in collecting resource use data. Safety results showed that adverse events were equally distributed across the regimens and a sensitivity analysis was done to assess the effect of including an assumed cost of adverse events on our conclusions. Other sensitivity analyses are described in subsequent subsections. All costs were adjusted to 2021 prices using country-specific consumer price indexes and converted to US$.[15,16]

Cost-utility analysis and cost-effectiveness analysis

EQ-5D-5L responses were converted into health-utility scores using the EuroQol validated tariff from the geographically nearest available country (Indonesia for India; Ethiopia for Ethiopia and Uganda; and Poland for Moldova).[6] Quality-adjusted life-years (QALYs) gained were calculated using the area under the curve approach and were used as an outcome for the cost-utility analysis (see appendix pp 8–9). Since baseline QALY measures can be prognostic of outcomes that are independent of treatment allocation,[17] we tested for between-group differences, planning to adjust before analysis if p value for the difference was less than or equal to 0·1.

Pooled (all seven trial countries) efficacy outcomes were used in the cost-effectiveness analysis b ecause these were powered to show the non-inferiority of the oral regimen to the control regimen, whereas country-specific estimates were not. For both the cost-utility and cost-effectiveness analyses, we calculated the incremental cost-effectiveness ratio (ICER), by dividing the between-group difference in mean total cost by the between-group difference in mean effect.

Decision uncertainty^ is presented using cost-effectiveness acceptability curves, which plot the ICER as a function of probability of cost-effectiveness against plausible willingness-to-pay (WTP) thresholds between US$0 and $20 000.[18] Cost-effectiveness acceptability curves were produced via bootstrapping, where we resampled 1000 estimates of mean costs and effects for each regimen.[17] The probability of being cost-effective was considered high if more than or equal to 80%. Cost-utility and cost-effectiveness analyses were done from the provider perspective and then from the societal perspective, by adding total participant costs to the provider costs.

Where one regimen was dominant (ie, cost less and delivered better outcomes), we report the dominant regimen. Where the intervention (oral or 6-month regimen) costs more and delivered better or similar outcomes than the control, we report the ICER and WTP threshold value where the cost-effectiveness acceptability

^*This paragraph in this paper version differs slightly to the published version due to thesis examiner clarification requests*

curve has an 80% probability of being cost-effective. To aid interpretation, WTP values in the cost-utility analysis are compared with the upper bound of published purchasing power parity adjusted cost per QALY-gained thresholds of $696 in Ethiopia, $2781 in India, $2400 in Moldova, and $725 in Uganda.[19]

Sensitivity and statistical analyses

All analyses were performed in Stata version 15.1. Participant costs are presented as means with their 95% CIs and p values. A difference was considered significant at the 95% significance level (p≤0·05). Deterministic sensitivity analyses were done on the following set of input parameters: bedaquiline costs, inclusion of adverse event costs, and the site-specific clinical efficacy outcome. Complete case analysis was done by excluding participants with incomplete responses. Some participant data were collected retrospectively in India and Uganda because of delayed in-country approvals. A sensitivity analysis excluding retrospectively collected data was done to identify the potential impact of recall bias. We also tested whether a change in the catastrophic expenditure threshold would affect the results. This trial is registered with ISRCTN, ISRCTN18148631.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, except that Janssen Pharmaceuticals provided a consultancy service upon request of the sponsor in relation to bedaquiline, the eligibility criteria, safety investigations, and the pharmacokinetic component to fulfil the regulatory requirements of the trial.

Results

All except two participants enrolled in the clinical trial in the four countries provided written informed consent and health economic data. Only eight participants in Moldova and nine participants in Uganda were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, analysis of the 6-month regimen was not done in these two countries. 300 participants were included in the economic analyses (Ethiopia, 61; India, 142; Moldova, 51; Uganda, 46). Participant characteristics and socioeconomic status at baseline are detailed in table 1.

Participant total direct costs were lower in the oral regimen group than in the control regimen group across all countries, apart from Uganda. Within direct costs, supplementary food was the main cost driver, with participants in the control regimen group spending more on supplements than those in the oral regimen group in Ethiopia, India, and Moldova, with the opposite finding in Uganda (tables 2, 3). Indirect participant costs were lower in the oral regimen group than the control group in Moldova and Uganda, and higher in the oral regimen group than the control group in Ethiopia and India. Total participant costs were lower in the oral regimen group than the control group in Moldova and Uganda, and higher in the oral regimen group than the control group in Ethiopia and India. Supplementary food expenditure was the main direct cost driver in the 6-month regimen group. Participants in the 6-month regimen group spent less on direct costs than those in the control group in both Ethiopia and India; the difference was statistically significant in India. Indirect participant costs were also lower for participants in the 6-month regimen group than in the control group in both countries. The proportion of

	Ethiopia				India				Moldova*			Uganda†		
	Control (n=21)	Oral (n=20)	6-month (n=20)	Total (n=61)	Control (n=46)	Oral (n=48)	6-month (n=48)	Total (n=142)‡	Control (n=25)	Oral (n=26)	Total (n=51)	Control (n=22)	Oral (n=24)	Total (n=46)‡
Sex														
Male	10 (48%)	11 (55%)	9 (45%)	30 (49%)	29 (63%)	16 (33%)	35 (73%)	80 (56%)	20 (80%)	19 (73%)	39 (76%)	13 (59%)	14 (58%)	27 (59%)
Female	11 (52%)	9 (45%)	11 (55%)	31 (51%)	17 (37%)	32 (67%)	13 (27%)	62 (44%)	5 (20%)	7 (27%)	12 (24%)	9 (41%)	10 (42%)	19 (41%)
Age (years)	29 (8·3)	31 (10·1)	28 (7·9)	29 (8·8)	35 (12·6)	38 (12·1)	36 (13·7)	36 (12·8)	40 (11·4)	38 (10·2)	39 (10·7)	35 (9·9)	33 (10·6)	34 (10·3)
HIV positive	0	2 (10%)	1 (5%)	3 (5%)	0	0	0	0	0	0	0	8 (36%)	9 (38%)	17 (37%)
Highest education level														
Illiterate	2 (10%)	2 (10%)	3 (15%)	7 (11%)	7 (15%)	9 (19%)	8 (17%)	24 (17%)	0	0	0	1 (5%)	0	1 (2%)
Primary	4 (19%)	4 (20%)	5 (25%)	13 (21%)	11 (24%)	19 (40%)	9 (19%)	39 (27%)	3 (12%)	2 (8%)	5 (10%)	11 (50%)	10 (42%)	21 (46%)
Secondary	7 (33%)	7 (35%)	8 (40%)	22 (36%)	21 (46%)	18 (38%)	22 (46%)	61 (43%)	19 (76%)	20 (77%)	39 (76%)	6 (27%)	12 (50%)	18 (39%)
Graduate	8 (38%)	7 (35%)	4 (20%)	19 (31%)	7 (15%)	2 (4%)	9 (19%)	18 (13%)	3 (12%)	4 (15%)	7 (14%)	4 (18%)	2 (8%)	6 (13%)
Primary income earner	8 (38%)	10 (50%)	11 (55%)	29 (48%)	18 (39%)	25 (52%)	23 (48%)	66 (46%)	17 (68%)	13 (50%)	30 (59%)	14 (64%)	16 (67%)	30 (65%)

Data are n (%) or mean (SD). *Only eight participants were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, no analysis of the 6-month regimen was done in Moldova. †Only nine participants were assigned to the 6-month regimen group; because this did not allow for meaningful comparison, no analysis of the 6-month regimen was done in Uganda. ‡Total number of participants included in India and Uganda is lower than the number of participants included in the clinical analysis. For logistical reasons, data collection for the health economic component was delayed in India and by the time we started participant interviews, one participant in the control group had died. In Uganda, one participant in the oral regimen group was younger than 18 years at the time of the interview, and thus excluded from our analysis.

Table 1: **Participant characteristics and socioeconomic status at baseline**

	Ethiopia						India					
	Control, mean*	Control, %†	Oral, mean*	Oral, %†	6-month, mean*	6-month, %†	Control, mean*	Control,%†	Oral, mean*	Oral, %†	6-month, mean*	6-month,%†
Direct costs (US$)												
Directly observed treatment cost‡	2·5 (0·37–4·53)	0·2%	2·2 (0·44–3·89)	0·1%	2·3 (0·39–4·25)	0·3%	11·6 (7·46–14·91)	0·8%	11·6 (7·64–15·13)	0·8%	8·6 (6·82–10·40)	0·7%
Assessment visit cost	19·8 (12·16–25·77)	1·2%	20·3 (14·12–26·39)	0·9%	39·6 (0·64–78·52)	4·4%	52·1 (42·22–61·99)	3·6%	56·2 (45·52–66·88)	3·9%	37·1 (30·70–43·40)	2·9%
Guardian cost	0·3 (0·00–0·73)	0	0·6 (0·00–1·21)	0	0·3 (0·00–0·66)	0	4·4 (1·56–7·22)	0·3%	4·1 (1·93–6·28)	0·3%	2·3 (0·96–3·65)	0·2%
Supplementary food	155·4 (71·52–239·27)	9·8%	133·0 (72·22–192·26)	5·9%	95·9 (31·80–160·01)	10·7%	224·2 (191·51–256·93)	15·7%	199·9 (167·60–232·20)	13·8%	186·4 (158·12–214·63)	14·4%
Total direct costs (US$)	178·0 (86·76–262·55)	11·2%	156·1 (89·51–216·69)	6·9%	138·1 (37·43–234·09)	15·5%	292·3 (248·80–312·64)	20·5%	271·8 (233·08–287·34)	18·7%	234·3 (196·44–255·02)	18·1%
Total indirect costs (US$)	1408·9 (110·32–2702·64)	88·8%	2091·7 (891·34–3292·15)	93·1%	755·6 (420·31–1090·83)	84·5%	1135·5 (811·68–1459·19)	79·5%	1179·9 (823·10–1536·58)	81·3%	1059·2 (656·28–1462·20)	81·9%
Total participant cost (US$)	1586·9	100%	2247·8	100%	893·7	100%	1427·8	100%	1451·7	100%	1293·6	100%
Incurred catastrophic costs (n)	17	81·0%	19	95·0%	18	90·0%	41	89·1%	40	83·3%	40	83·3%
p value (oral or 6-month costs *vs* control costs)												
Direct costs	NA	NA	0·68	NA	0·54	NA	NA	NA	0·33	NA	0·0098§	NA
Indirect costs	NA	NA	0·43	NA	0·33	NA	NA	NA	0·84	NA	0·77	NA

NA=not applicable. *Data are mean (95% CI), apart from in rows showing incurred catastrophic costs (number) and p values. †As a percentage of total costs. ‡Costs of directly observed treatment comprised transport and food, and for a very small number of participants (n=12) in India, a fee to get the injectable treatment at private facilities during weekends when public facilities were closed. For the rest of the participants treatment was free. §Statistically significant.

Table 2: **Participant direct, indirect, total, and catastrophic costs for each regimen (baseline to week 76), in Ethiopia and India**

participants facing catastrophic costs within the trial was high (81% or more) in all regimen groups and countries (tables 2, 3).

Total provider cost was higher in the oral regimen group than the control group in all countries (figure 1; appendix pp 16–17; for unit costs used see appendix pp 18–22). The difference in mean total cost per participant in the oral and control regimen groups (oral minus control) was $538·1 (95% CI 419·5–656·8, p<0·0001) in Ethiopia, $205·9 (102·0–309·1, p<0·0001) in India, $234·0 (187·0–653·7, p=0·27) in Moldova, and $725·4 (336·7–1113·3, p=0·00070) in Uganda. There were some provider cost savings in outpatient visit and staff cost categories in the oral regimen group compared with the control group, but these did not offset the higher regimen medication costs in the oral regimen group. Moreover, in terms of monitoring tests, the major cost drivers were laboratory tests required for monitoring both oral and injectable-containing regimens; the injectable-regimen-specific monitoring tests were not a major cost driver (appendix pp 11, 20–21). In the clinical trial, there were more participants reporting hearing loss as a serious adverse event in the control group than in the oral regimen group. Hearing loss serious adverse events were estimated to cost $34·6 per participant, so the oral regimen would still be costlier (appendix p 10). A full course of bedaquiline in the oral regimen group accounted for 15% of total provider cost in Ethiopia, 26% in India, 15% in Moldova, and 9% in Uganda (appendix pp 16–17). Duration of inpatient stay varied widely across the four countries (from 10·7 days to 125·0 days) and regimens (30 days to 59 days) with correspondingly variable inpatient stay costs (appendix p 22). Total provider cost was lower in the 6-month regimen group than the control group in both Ethiopia and India. The difference in mean total cost per participant treated (6-month minus control) was –$291·0 (95% CI –189·6 to –391·9, p<0·0001) in Ethiopia and –$47·7 (–135·9 to 38·7, p=0·27) in India. Outpatient visit, staff, and monitoring test costs were lower, while regimen medication costs were higher, in the 6-month regimen group versus the control regimen group (appendix pp 16–17).

Mean incremental QALYs were not adjusted for baseline differences, because no such differences were found.[20] Compared with the control regimen, the oral regimen was associated with more mean QALYs over the 76 weeks of follow-up in Moldova (0·92 *vs* 0·96, p=0·28), fewer QALYs in India (0·76 *vs* 0·74, p=0·72) and Uganda (0·73 *vs* 0·69, p=0·19), and the same QALYs in Ethiopia (0·90 *vs* 0·90, p=0·69). Compared with the control regimen, the 6-month regimen resulted in the same QALYs in Ethiopia (0·90 *vs* 0·90, p=0·75) and more QALYs in India (0·76 *vs* 0·79, p=0·29; table 4). Across all trial sites, a pooled favourable outcome was achieved by 162 (83%) of 196 participants in the oral regimen group, 122 (91%) of 134 participants in the 6-month regimen group,

	Moldova				Uganda			
	Control, mean*	Control, %†	Oral, mean*	Oral, %†	Control, mean*	Control, %†	Oral, mean*	Oral, %†
Direct costs (US$)								
Directly observed treatment cost‡	4·3 (1·67–7·01)	0	4·0 (0·00–8·12)	0·1%	6·1 (3·27–8·86)	0·2%	11·0 (7·17–14·80)	0·5%
Assessment visit cost	62·7 (35·25–90·10)	0·5%	72·8 (52·64–92·90)	1·0%	104·1 (85·55–122·66)§	3·7%	117·0 (102·26–131·81)§	5·4%
Guardian cost	0	0	0	0	0·9 (0·00–2·00)	0	1·6 (0·00–4·06)	0·1%
Supplementary food	75·4 (36·41–114·34)	0·6%	39·7 (0·00–79·66)	0·6%	101·2 (81·26–121·06)	3·6%	117·6 (78·82–156·31)	5·4%
Total direct costs (US$)	142·3 (100·90–183·87)	1·2%	116·4 (72·77–160·14)	1·6%	212·2 (187·35–224·86)	7·6%	247·3 (197·99–274·47)	11·4%
Total indirect costs (US$)	11 516·3 (6069·33–16 963·18)	98·8%	6942·7 (3817·36–10 068·14)	98·4%	2575·3 (1641·32–3509·40)	92·4%	1928·9 (942·26–2915·61)	88·6%
Total participant cost (US$)	11 658·6	100%	7059·1	100%	2787·5	100%	2176·2	100%
Incurred catastrophic costs (n)	23	92·0%	25	96·2%	21	95·5%	20	83·3%
p value (oral or 6-month costs *vs* control costs)								
Direct costs	NA	NA	0·38	NA	NA	NA	0·16	NA
Indirect costs	NA	NA	0·14	NA	NA	NA	0·30	NA

NA=not applicable. *Data are mean (95% CI), apart from in rows showing incurred catastrophic costs (number) and p values. †As a percentage of total costs. ‡Costs of directly observed treatment comprised transport and food, and for a very small number of participants (n=12) in India, a fee to get the injectable treatment at private facilities during weekends when public facilities were closed. For the rest of the participants treatment was free. §Because recruitment catchment area was extended towards the end of the trial, more participants in the all-oral group were living further from the hospital, having to use a means of transport for attending participant follow-up visits, on average, for an additional 12 minutes compared with the control group. Because this difference was not related to the treatment allocation, we used pooled mean transport costs for both regimens to calculate total assessment visit costs. The difference in cost is given by the different number of visits and food purchases on the day.

Table 3: **Participant direct, indirect, total, and catastrophic costs for each regimen (baseline to week 76), in Moldova and Uganda**

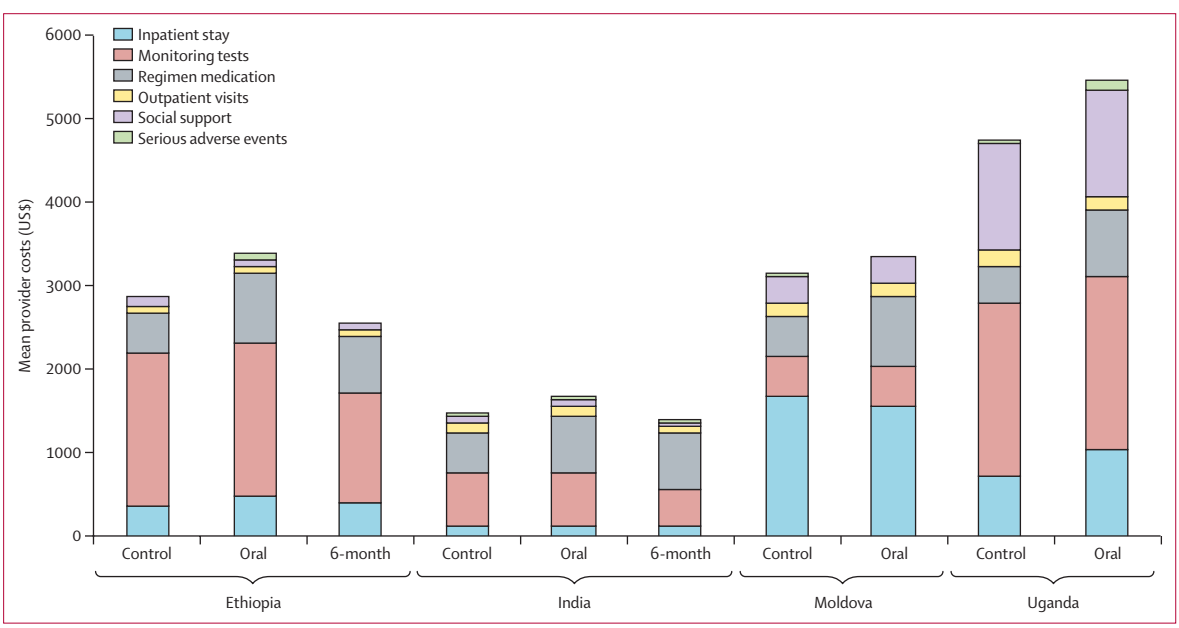

Figure 1: **Mean provider costs by regimen, cost category, and country**

and 133 (71%) of 187 participants in the control regimen group. The oral regimen was superior in efficacy to the control regimen.[7]

From the provider perspective, the oral regimen resulted in higher provider costs and the same or lower QALYs in Ethiopia, India, and Uganda, meaning that it is not cost-effective, and the control regimen dominates (table 4 and figure 2A). In Moldova, the oral regimen cost more and resulted in more QALYs; however, the ICER ($5965) exceeds the upper bound of the Moldovan WTP threshold of $2400 per QALY, and the cost-effectiveness acceptability curve does not meet the 80% threshold within the WTP range tested, thus suggesting that the oral regimen is not cost-effective in Moldova (table 4 and figure 2A). Adoption of a societal perspective does not change the results for Ethiopia, India, and Uganda,

	Total costs by perspective (US$) and QALYs				Interpretation	
	Provider	Participant	Societal	QALYs	Provider	Societal
Ethiopia						
Oral	3378·1	2247·8	5625·9	0·8981	..	..
6-month	2549·0	893·7	3442·7	0·9002	..	..
Control	2876·6	1586·9	4463·5	0·9050	..	..
Difference: control *vs* oral	501·5	660·9	1162·4	–0·0068	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)
Difference: control *vs* 6-month	–327·6	–693·2	–1020·8	–0·0047	6-month costs less and yields slightly fewer QALYs; ICER *vs* WTP: $68 530·6 *vs* $686, 6-month is considered cost-effective because the magnitude of the cost-saving is large, whereas the magnitude of the QALY reduction is very small (bottom-left quadrant of the cost-effectiveness plane)	6-month costs less and yields slightly fewer QALYs; ICER *vs* WTP: $205 818·5 *vs* $686, 6-month is considered cost-effective because the magnitude of the cost-saving is large, whereas the magnitude of the QALY reduction is very small (bottom-left quadrant of the cost-effectiveness plane)
India						
Oral	1628·0	1451·7	3079·7	0·7439	..	..
6-month	1374·7	1293·6	2668·0	0·7932	..	..
Control	1422·1	1427·8	2849·9	0·7644	..	..
Difference: control *vs* oral	205·9	23·9	229·8	–0·0205	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)
Difference: control *vs* 6-month	–47·4	–134·2	–181·9	0·0288	6-month dominant (costs less and yields more QALYs)	6-month dominant (costs less and yields more QALYs)
Moldova						
Oral	3362·9	7059·1	10 422·0	0·9627	..	..
Control	3128·9	11 658·6	14 787·5	0·9235	..	..
Difference: control *vs* oral	234·0	–4599·5	–4365·5	0·0392	Oral costs more and yields more QALYs; ICER *vs* WTP: $5965·5 *vs* $2400, hence oral unlikely to be cost-effective	Oral dominant (costs less and yields more QALYs)
Uganda						
Oral	5437·9	2176·2	7614·1	0·6937	..	..
Control	4712·5	2787·5	7500·0	0·7343	..	..
Difference: control *vs* oral	–725·4	–611·3	–114·1	–0·0406	Control dominant (costs less and yields more QALYs)	Control dominant (costs less and yields more QALYs)

ICER=incremental cost-effectiveness ratio. QALYs=quality-adjusted life-years. WTP=willingness-to-pay.

Table 4: **Provider costs, QALYs, ICERs, and interpretation against WTP threshold by country, regimen, and perspective**

because the oral regimen still results in higher costs and the same or lower QALYs than the control regimen in these countries (table 4 and figure 2C). However, in Moldova, the oral regimen results in lower societal costs (because of substantially lower participant costs) and higher QALYs, making the oral regimen dominant and cost-effective (table 4 and figure 2C).

From the provider-perspective cost-effectiveness analysis, the oral regimen has a high (80%) probability of being cost-effective compared with the control regimen if the WTP thresholds for each additional favourable outcome are more than $4500 in Ethiopia, more than $1900 in India, more than $3950 in Moldova, and more than $7900 in Uganda (figure 2B). From a societal perspective, the WTP thresholds must exceed $15 900 in Ethiopia, $3150 in India, and $4350 in Uganda for the oral regimen to have a high probability of being cost-effective (figure 2D). In Moldova, the oral regimen results in lower costs and additional favourable outcomes versus the control regimen, so it is dominant and cost-effective.

In Ethiopia, the 6-month regimen had lower provider and societal costs and very similar QALYs versus the control regimen. There is a high probability that the 6-month regimen is cost-effective against published Ethiopian threshold estimates of $686 per QALY. In India, the 6-month regimen also resulted in lower provider and societal costs, and higher QALYs, making it dominant and cost-effective (table 4, figure 3A, C). The 6-month regimen had more favourable outcomes than the control regimen in both Ethiopia and India, making the 6-month regimen dominant and cost-effective from both perspectives (figure 3B, D).

Results were sensitive to the cost of bedaquiline. A reduction in the price per 100 mg pill from $1·81 to $1·00 (appendix pp 25–26) would make the oral regimen cost-effective in India (ICER $1018 < WTP threshold $2781) and Moldova (ICER $517 < WTP threshold $2400) from a provider-perspective cost-utility analysis. Making the same change to bedaquiline pricing, the cost-effectiveness analysis shows that the oral regimen would dominate the control regimen in India from a provider perspective and have a high probability of being cost-effective from a societal perspective. The oral regimen would also have a high probability of being cost-effective in Moldova from the provider perspective (and become

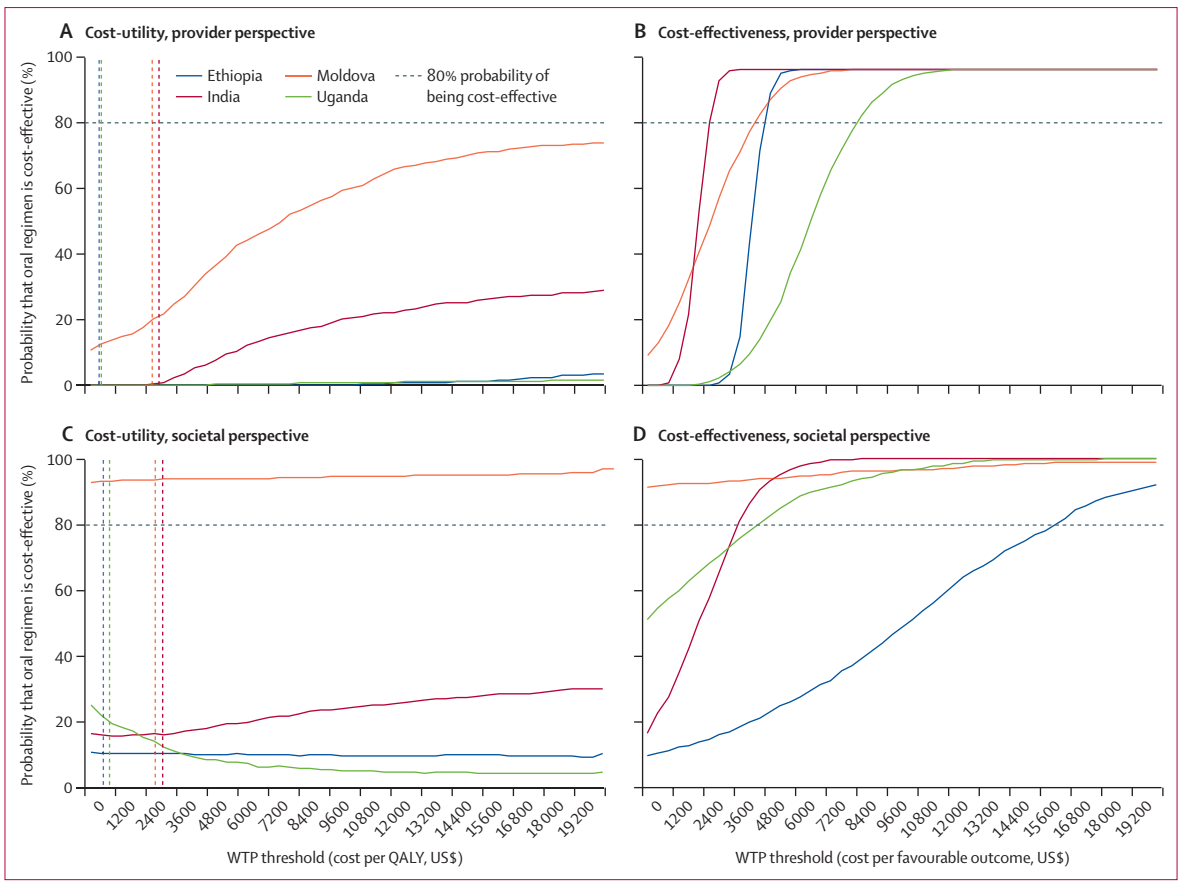

Figure 2: **Cost-effectiveness acceptability curves from the economic evaluation of the oral regimen versus control regimen**
The solid lines plot country-specific cost-effectiveness or cost-utility probabilities as derived from our 1000 bootstrapped estimates of mean incremental costs and effects for the oral regimen compared with the control regimen. To aid interpretation, the horizontal dashed grey line on each panel illustrates our (arbitrary) threshold of 80% that we deem a high probability of being cost-effective. In the cost-utility analysis panels (A and C), empirically derived, country-level WTP per QALY thresholds from the literature[19] are shown using vertical-dashed blue (Ethiopia, US$686 per QALY), red (India, $2781 per QALY), orange (Moldova, $2400 per QALY), and green (Uganda $725 per QALY). Decision makers may have their own thresholds for both uncertainty and WTP. In the cost-effectiveness analysis panels (B and D), since favourable outcome as used in this study is not a standard health outcome, there are no available published thresholds to present, and instead we report the value where the cost-effectiveness estimates cross the 80% probability threshold. (A) The probability does not exceed 80% in any country for any WTP per QALY threshold, hence the oral regimen is not cost-effective. (B) The probability exceeds 80% for WTP per additional favourable outcome thresholds of more than $4500 in Ethiopia, more than $1900 in India, more than $3950 in Moldova, and more than $7900 in Uganda. (C) The probability exceeds 80% in Moldova for all WTP per QALY thresholds, hence the oral regimen is considered cost-effective. In Ethiopia, India, or Uganda, the probability does not exceed 80% for any WTP per QALY threshold, hence the oral regimen is not cost-effective. (D) The probability exceeds 80% for WTP per additional favourable outcome thresholds of more than $15 900 in Ethiopia, more than $3150 in India, and more than $4350 in Uganda. In Moldova, the probability exceeds 80% for all WTP thresholds. WTP=willingness-to-pay. QALY=quality-adjusted life-year.

more attractive). The 6-month regimen would be even more attractive in relation to the WTP thresholds (appendix pp 25–26).

When the country-specific efficacy outcome (instead of the pooled estimates) was used in the provider-perspective cost-effectiveness analysis, the ICERs decreased in India, Moldova, and Uganda, suggesting that the oral regimen became more attractive than in the base case. In the societal-perspective analysis, the oral regimen remained dominant in Moldova, while the ICERs decreased in Uganda and increased in India. In Ethiopia, from either perspective, the ICERs increased, making the oral regimen less attractive than in the base case (appendix pp 25–26). The 6-month regimen would continue being dominant (and cost-effective) in both Ethiopia and India.

The proportion of participants who provided complete data was 48 (79%) of 61 in Ethiopia, 139 (98%) of 142 in India, 51 (100%) of 51 in Moldova, and 43 (93%) of 46 in Uganda. Using complete case analysis, the mean cost per participant increased overall, but this had no effect on the cost-utility conclusions (appendix pp 25–26). Results remained robust to exclusion of retrospectively collected data in India and Uganda, and an increase of up to $150 per participant to treat adverse events (while mean cost per participant to treat a serious adverse event was $18). A high proportion of participants (69% or higher) still had catastrophic costs when the catastrophic

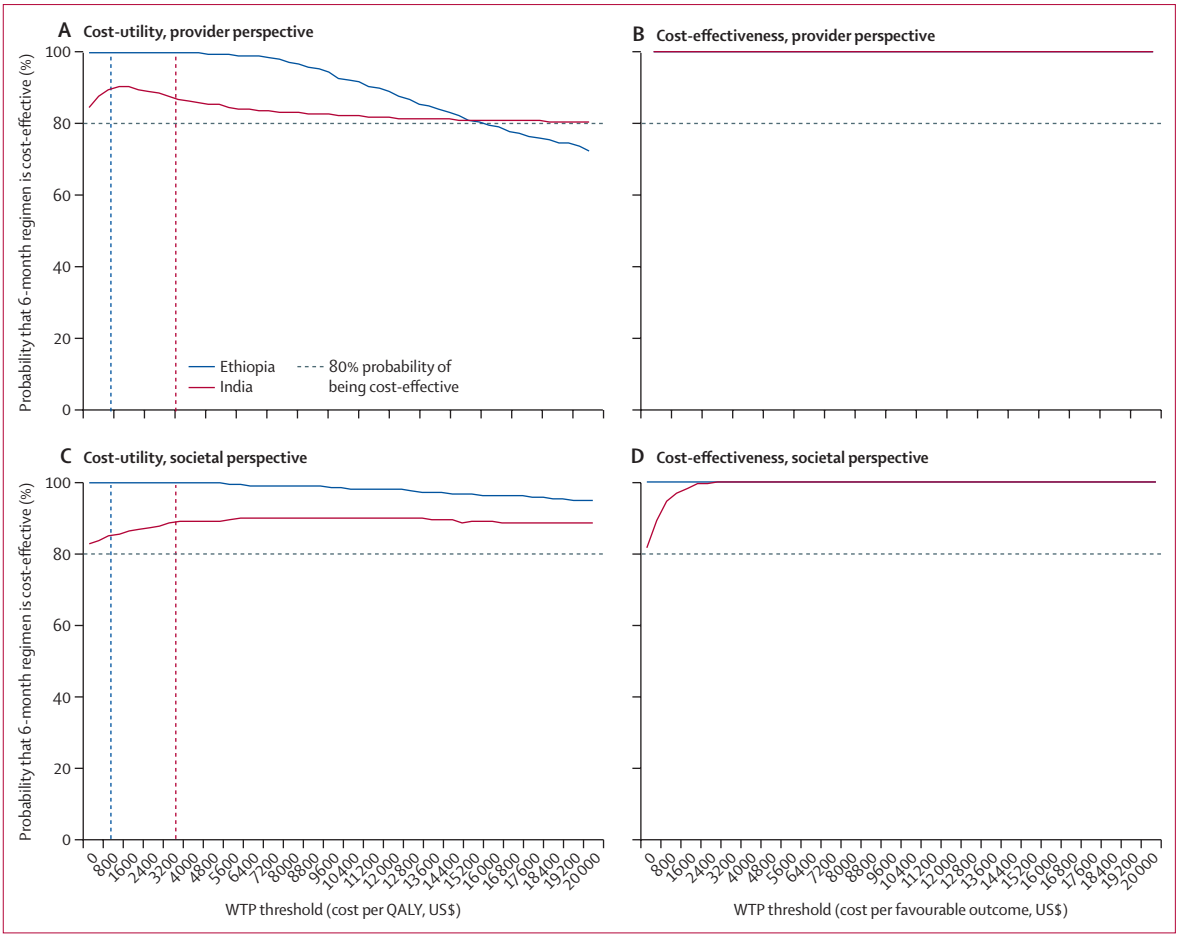

Figure 3: **Cost-effectiveness acceptability curves from the economic evaluation of the 6-month regimen versus control regimen**
The solid lines plot country-specific (insufficient data for comparison in Moldova and Uganda) cost-effectiveness or cost-utility probabilities as derived from our 1000 bootstrapped estimates of mean incremental costs and effects for the 6-month regimen compared with the control regimen. To aid interpretation, the horizontal dashed grey line on each panel illustrates our (arbitrary) threshold of 80%, which we deem a high probability of being cost-effective. Decision makers may have their own threshold. In the cost-utility analysis panels (A and C), empirically derived, country-level WTP per QALY thresholds from the literature[19] are shown using vertical-dashed blue (Ethiopia, US$686 per QALY) and red (India, $2781 per QALY). Decision makers may have their own thresholds for both uncertainty and WTP. In the cost-effectiveness analysis panels (B and D), since favourable outcome as used in this study is not a standard health outcome, there are no available published thresholds to present and instead, we report the value where the cost-effectiveness estimates cross the 80% probability threshold. (A, C) In Ethiopia, the probability exceeds 80% at the empirical WTP per QALY threshold of $686 and up to $15 600, hence the 6-month regimen is cost-effective within that WTP range. In India, the probability exceeds 80% at the empirical WTP per QALY threshold of $2781 and up to more than $20 000, hence the 6-month regimen is cost-effective within that WTP range. (B, D) In Ethiopia and India, the probability exceeds 80% for all WTP per additional favourable outcome threshold values, hence the 6-month regimen is cost-effective. Note, in B, lines are directly on top of each other, so only one can be seen. WTP=willingness-to-pay. QALY=quality-adjusted life-year.

expenditure threshold was increased from 20% to 60% of participants' individual income (appendix pp 27–28).

Discussion

This within-trial economic evaluation compared an oral regimen for the treatment of rifampicin-resistant tuberculosis, as recommended by WHO in 2020, with an injectable-containing regimen (control) in widespread use when STREAM stage 2 began in 2016. The results of the provider-perspective cost-utility analysis showed that the ICERs exceeded realistic WTP per additional QALY thresholds in all countries. These findings were upheld in the societal-perspective analysis, except in Moldova, where the oral regimen was cost-effective from a societal perspective. The trial endpoint (favourable outcome) used in the cost-effectiveness analysis is difficult to interpret because of the absence of any revealed WTP data on it, and difficult to meaningfully compare with other outcomes (because of practical challenges in calculating the costs and consequences of favourable or unfavourable outcome). Nevertheless, it seems unlikely that country tuberculosis programmes would be willing to pay the amounts estimated by our bootstrap analysis (ie, for the oral regimen to have a probability ≥80% of being cost-effective), which ranged from $1900 to $7900 per additional favourable outcome. In the two countries (Ethiopia and India) for which we had data to make a comparison, we found that treating rifampicin-resistant

tuberculosis with the 6-month regimen is highly likely to be cost-effective, regardless of economic evaluation method or perspective.

Bedaquiline costs were an important cost driver in the oral regimen, accounting for 15% of total provider costs in Ethiopia and Moldova, 26% in India, and 9% in Uganda. Importantly, sensitivity analyses showed that a reduction in bedaquiline costs would make the oral regimen cost-effective in India and Moldova (though not in Ethiopia and Uganda) in the provider-perspective cost-utility analysis, and highly likely to be cost-effective in Moldova and dominant in India in the provider-perspective cost-effectiveness analysis. For the 6-month regimen, the bedaquiline costs were offset because the shorter treatment duration resulted in lower provider costs overall.

Although the empirically derived WTP per QALY threshold estimates used (from 2013) might be different today,[19] both sets of economic evaluation results were presented together with the cost-effectiveness acceptability curves to allow for interpretation across a range of possible thresholds. Decision makers are encouraged to consider their outcomes of interest (QALYs or improved efficacy), WTP, and how sure they want to be about the decision, alongside additional factors (not captured within this economic evaluation), such as patient and community perceptions about injectables, to make context-specific decisions on which regimens to implement within a transparent decision-making process.[21,22]

Given the importance of patient-centred care in tuberculosis, a key strength of the STREAM trial is that we collected health-related quality of life data directly from participants in receipt of different regimens, whereas most previous studies have used disability-adjusted life-years or QALY estimates from the literature. This difference compromises our ability to compare our empirical results directly with other economic evaluations; however, our conclusions contrast with most existing studies, which suggest that all-oral regimens are cost-effective or cost-saving when compared with an injectable regimen of the same duration,[23,24] for the reasons discussed later in this report.

Most previous studies used data from a phase 2b trial, which showed that addition of bedaquiline to an existing treatment regimen for rifampicin-resistant tuberculosis reduced the median time to culture conversion and increased the rate of culture conversion (ie, clinical cure) at 24 weeks compared with the addition of placebo (79% *vs* 58%, difference 21%).[25] Provider and patient costs were then modelled, based on these outcomes, with the proportion of patients achieving culture conversion strongly influencing economic findings. A systematic review indicated that these and other inputs, such as a lower number of patients reporting adverse events, were responsible for the reduced treatment and patient costs in the bedaquiline-containing group. Within STREAM, we measured the median time to culture conversion, and found no significant differences between regimens; moreover, the difference in the percentage of participants achieving a favourable outcome in control versus oral regimen groups was substantially lower in STREAM (11%) than in the phase 2b trial (21%).[7,25] We also observed how these clinical outcomes affected costs. Regarding adverse events, in STREAM, there was no suggestion of between-group differences in the proportion of participants who had a serious adverse event, treatment-related serious adverse event, or grade 3 or 4 adverse events.[7]

WHO recommends mainly outpatient rather than inpatient care for patients with rifampicin-resistant tuberculosis, and this model was followed in all our trial sites apart from Moldova.[26] Unlike the control regimen, the oral regimen does not require administration of injectable drugs for 112 days, and thus would potentially be more suited to outpatient-based delivery than the control regimen, with potential economic savings and benefits to providers and patients. However, we found that duration of inpatient stay was influenced by the need to monitor severely ill patients and that sites chose their duration of inpatient care according to local circumstances, rather than regimen allocation, suggesting that these economic benefits would not necessarily arise.

Modelling carried out for the WHO 2020 guidelines suggested that injectable-containing regimens carried the additional costs of managing injectable-related adverse events, which would potentially be reduced when moving to an oral regimen, improving cost-effectiveness.[4] However, we showed that within the monitoring tests, the major cost drivers were laboratory tests required for monitoring both oral and injectable-containing regimens (sputum smear and culture, liver function tests, lactate dehydrogenase, and pancreatic amylase) and that the injectable-regimen-specific monitoring costs (audiometry and renal function) were not a major cost driver.

Ending the tuberculosis epidemic requires the implementation of socioeconomic interventions. Two findings from our study will be useful in designing social protection packages for patients with tuberculosis. First, despite provision of social support payments for all participants, the majority on all regimens had catastrophic costs. Second, supplementary food expenditure was an important participant cost driver. Although supervising clinicians offered the same advice to all participants, those in the control regimen group reported higher supplementary food expenditure across all countries, apart from Uganda, where this is being investigated qualitatively.

Time horizon is crucial in economic evaluations. An insufficiently long time horizon might fail to capture outcomes accurately and lead to biased results; however, modelling a longer time horizon beyond the trial's measured endpoints increases assumptions and uncertainty, indicating a trade-off. The results reported

here cover the period from randomisation to week 76, which includes a 36-week follow-up beyond the treatment end date for the oral and control regimens, and 48-week follow-up for the 6-month regimen. We contend that this time horizon is sufficiently long to have captured any non-trivial between-group differences in costs, treatment outcomes, or treatment-related serious adverse events that would affect patients' health-related quality of life or survival or death rates in the longer term, with one possible exception being hearing loss. Exploring this event from the provider perspective showed that managing the additional hearing loss in the control group would not change our conclusions. We recognise that this analysis does not capture the wider effects of hearing loss on ability to work (and therefore participants' economic outcomes) and plan to conduct further analysis of longer-term costs and outcomes (positive and negative [eg, from serious adverse events]) on participants once follow-up data to week 132 are available. A further potential limitation in relation to hearing loss is that the literature suggests that EQ-5D-3L performs poorly in conditions involving hearing disorders.[27] Although we used the (likely more sensitive) EQ-5D-5L, it remains possible that this questionnaire might not have fully captured the benefits of an oral regimen. We have also not included the effect of permanent disability on income beyond week 76. To model this would have required country-specific data on the state of labour markets and levels of participation by individuals after treatment completion who have been in receipt of the alternative treatment regimen, and this was beyond the scope of the current analysis.

Transferability of findings from within-trial economic evaluation, and trials in general, can be challenging. For example, in this study, participants' visits for trial monitoring might have been more frequent than under programmatic conditions, especially for visits after treatment completion, potentially increasing direct costs. However, the number of visits was balanced across trial groups and participant costs for attending the trial assessment visits are less than 5% of the total participant cost, so this is unlikely to have affected the conclusions. Given the trial setting, it is possible that clinicians noted the early signs of some adverse events before evolution into serious adverse events, thus underestimating provider costs expected under routine conditions. Again, this would be balanced across groups. We have tried, wherever possible, to approximate usual care in our analysis, and thus we included trial regimen costs, salvage regimen costs, and additional medication costs that would occur outside the trial setting. In some cases, we used private rather than public facility costs to calculate provider costs; although this is unlikely to affect between-group comparisons, it might overestimate total costs, hence readers are invited to consider the detailed unit costs presented in relation to their own context.

In a May 2022 rapid communication, WHO announced that forthcoming guidelines will include recommendations for programmatic use of a 6-month all-oral regimen and a 9-month all-oral regimen for rifampicin-resistant tuberculosis.[1] Economic evaluation data from clinical trials on these regimens are not in the public domain, but both regimens contain bedaquiline and new drugs (eg, pretomanid), requiring providers to carefully consider these costs when planning implementation.

Rifampicin-resistant tuberculosis is a disease that affects approximately 500 000 people per year. Our results provide robust evidence on the cost-utility and cost-effectiveness of two new rifampicin-resistant tuberculosis regimens under trial conditions and aim to guide uptake and implementation of regimens in-country by providing crucial information on the potential costs, savings, and patient-reported outcomes. These results (and their limitations) indicate that further work is needed to enable cost-effective delivery of 9-month bedaquiline-based regimens, and that the 6-month bedaquiline-based regimen represents a cost-effective alternative—if injectable use for 2 months is acceptable for patients, providers, and policy makers. The results also provide crucial information for use in designing financial protection packages for patients, at a time when the world has recently missed the 2020 milestone of 0% tuberculosis-affected households facing catastrophic costs.

Contributors

LR made a substantial contribution to the conception and design, organisation, and conduct of the study. She supervised data collection in all countries, contributed to data collection, and carried out data cleaning, analysis, and interpretation. She designed the figures and tables, produced the first draft of the manuscript, and incorporated critical feedback and revisions from coauthors. JJM made a substantial contribution to study conception and design, analysis, and interpretation. He also helped with the conduct of the study and critiqued the manuscript for important intellectual content. EMT helped with the conduct of the study in Uganda, interpretation of the overall results, and critiqued the manuscript for important intellectual content. MM, JN, MG, VV, PB, and RD supervised participant data collection and provider costing data at their respective sites in Chennai, Uganda, Ethiopia, Moldova, Delhi, and Ahmedabad, and provided their input when needed. MM also critiqued the manuscript for important intellectual content. AKBa, DM, GN, RS, AKBh, ET, and BK were the principal investigators of the health economic analysis sites and were involved in trial data collection. AKBa, DM, GN, and ET critiqued the manuscript for important intellectual content. SKM is the co-chief investigator of the clinical trial. She made data from the clinical trial available to us, classified the serious adverse events for the health economic analysis, and critiqued the manuscript for important intellectual content. AJN is the co-chief investigator of the clinical trial. He made data from the clinical trial available to us and critiqued the manuscript for important intellectual content. GB contributed to the data interpretation and critiqued the manuscript for important intellectual content. She also helped with the project administration. IDR together with SBS conceived and planned the presented study and were the investigators with most responsibility for securing funding. They both critiqued the manuscript for important intellectual content. SBS made a substantial contribution to the organisation, conduct, and supervision of the study and to data analysis and interpretation. He contributed to drafting the manuscript. EW contributed substantially to the study design, supervised data collection, and contributed substantively to the analysis, data interpretation, and writing of this

manuscript and critiqued it for important intellectual content. All authors have read and approved the final version of the manuscript for submission. MG accessed and verified the data in Ethiopia, MM in India, VV in Moldova, and JN in Uganda. LR accessed and verified the data across all sites. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LR reports consulting fees from GSK (paid to institution) and support for attending trial-related meetings from Janssen Research & Development and the US Agency for International Development (USAID; paid to institution). JJM reports support for attending meetings or travel from the Liverpool School of Tropical Medicine. EMT reports consulting fees from GSK (paid to institution) and support for attending meetings from USAID (paid to institution). MM, PB, RD, GN, AKBh, BK, SKM, AJN, GB, IDR, and EW report support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution). ET reports support for attending meetings from USAID (paid to institution). SBS reports a research grant on tuberculosis research (paid to institution) from the UK Foreign & Commonwealth Development Office, support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution), and is co-chair of the Scientific Working Group on Implementation Research for the Tropical Disease Research Foundation (unpaid). All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available no later than 12 months after the end of the trial via the TBPACT data repository (https://c-path.org/programs/tb-pacts/). We will provide deidentified participant data, data dictionary, study protocol, a set of blank case record forms, and the informed consent form.

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Supplementary appendix^

Supplement to: Within-trial economic evaluation of shortened, bedaquiline-containing treatment regimens for MDR/RR-TB evaluated in STREAM Stage 2

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^Indicates that this supplementary appendix version and the published version differ slightly due to thesis examiner clarification requests

1.0 CONTENTS

2.0 List of abbreviations

AHRI- Armauer Hansen Research Institute

CHEERS- Consolidated Health Economic Evaluation Reporting Standards

CRF- Clinical Report Form

DOT- Directly observed treatment

GF- Global Fund

GHC- Global Health Committee

IMSP- Phthisiopneumology Institute 'Chiril Draganiuc'

MDR-TB- Multidrug resistant tuberculosis

MoH- Ministry of Health

RR-TB- Rifampicin resistant tuberculosis

SAE- Serious Adverse Event

STREAM- The Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB

TB- Tuberculosis

3.0 Listing of Supplementary Tables and figures

Table S1: Consolidated Health Economic Reporting Standard checklist

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4.0 STREAM STUDY TEAM AND ADDITIONAL ACKNOWLEDGEMENTS

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5.0 DETAILED METHODS

Health economic data was collected in four out of seven STREAM trial countries. There were seven health economic sites across the four countries, with treatment being administered within the existing public-health facilities at:

- Armauer Hansen Research Institute (AHRI), Addis Ababa, Ethiopia
- St. Peter's Hospital, Addis Ababa, Ethiopia
- B.J. Medical College, Ahmedabad, India
- National Institute for Research in Tuberculosis, Chennai, India
- Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, Delhi, India
- IMSP, Chiril Draganiuc, Chisinau, Moldova
- Mulago Hospital, Kampala, Uganda

All costs are reported in 2021 USD, assuming exchange rates of 49.8 Birr, 74.5 INR, 18.2 MDL and 3571.4 UGX to 1 USD.[1] Capital costs extending beyond one year (e.g. equipment) were annualised over an expected lifespan of five years using a discount rate of 3%.

Local health economists at each site received data collection training and guidance from the study leads.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used as a guide to optimise the preparation and reporting of the manuscript (Table S1).[2]

The Six-month vs. Control analysis was only conducted in Ethiopia and India. In Ethiopia, recruitment to the Six-month regimen was stopped early, when 19 participants were enrolled in the Control regimen. We have not conducted a concurrent control analysis as the number of participants enrolled in the Control regimen after recruitment to the Six-month regimen stopped was low (two participants) and because we do not expect the economic circumstances and care seeking behaviour of these two participants to be different to the other 19 participants.

The Control regimen comprised of moxifloxacin (at higher-than-standard dose), clofazimine, ethambutol and pyrazinamide given for 40 weeks, with kanamycin, high-dose isoniazid and prothionamide given during the 16-week intensive phase. In 2018, the levofloxacin was replaced by moxifloxacin. The Oral regimen is the same as Control, except that kanamycin is replaced by bedaquiline that is administered for the 40 weeks duration of the regimen, and moxifloxacin is replaced by levofloxacin. The Six-month regimen comprised of bedaquiline, clofazimine, pyrazinamide and levofloxacin prescribed for 28 weeks, supplemented by high-dose isoniazid and kanamycin for the intensive phase by 4 or 8 weeks in the event of delayed sputum smear conversion. The dosing of the drugs was not fixed and was dependent on the patients' weight. More details are available in the clinical manuscript.[3]

The Control regimen approximated to standard of care in all countries for most of the trial duration as it was recommended by WHO since 2016. The last patient was enrolled in STREAM Stage 2 in January 2020, shortly before WHO recommended a 9-month bedaquiline-containing injectable-free regimen based on 'very low certainty' evidence.[3]

The trial inclusion criteria required participants to have microbiologically-confirmed pulmonary tuberculosis with evidence of resistance to rifampicin, regardless of susceptibility to isoniazid, and without fluoroquinolone or aminoglycoside resistance.

5.1 PROVIDER COSTING

Total provider costs by category are in table S2.

A health system costing spreadsheet was developed by the study leads and shared with the focal health economists in all countries. The health economic teams reviewed on-site trial documentation, national tuberculosis (TB) guidelines and consulted the trial principal investigator in each country to complete the spreadsheet.

Time and motion studies and interviews with the health workers were conducted at each site to identify the duration of patient assessment visits, staff involved, consumables, tests and equipment used. Each unit of resource used was then multiplied by their respective unit cost and frequency. Tables S3, S4 and S5 and S6 contain the unit prices used (and their sources) in this costing analysis. These represented the 2021 local prices, exchanged into dollars using the exchange rates above, collected by the focal health economists in each country.

Staff costs were calculated by multiplying the number of minutes spent with the participant (as reported during the staff interviews) with the midpoint for the national pay range of the relevant grade of staff (as revealed in the time and motion studies) (table S3) (from hospital financial or government records).

In calculating monitoring test costs (laboratory tests, ECG and audiometry), we assumed that each participant attended their assessment visit and had all tests performed according to the protocol; laboratory safety tests were done four times during the intensive phase (IP) and six times during the continuation phase (CP) for the Control and Oral regimens, and twice in the IP and five times in the CP for the Six-month regimen. The visit frequency during treatment did not substantially differ from national guidelines in Ethiopia, Moldova and Uganda, however, post-treatment follow-up visits did. Depending on the country, the assessment visits after treatment end varied from no visits (in India) to four visits (in Moldova) compared to 11 visits in the study.

We used the trial CRFs to calculate the number of days each medication was administered; this took into account any dosage adjustments, treatment interruptions, additional drugs added to the regimen, or change to salvage regimens. Total number of each pill was then multiplied by the Global Drug Facility unit prices from the medicines catalogue[4], taking into account their respective dosages.

Aggregated data from the financial department records were used to calculate inpatient stay costs in Moldova. Total hospital expenditure related to inpatient stay was then divided by the number of inpatient stay days for the MDR-TB patients. Where these data were not available to us, we used private hospital stay costs. In addition to this, in Ethiopia and India market prices were used to cost the meal offered to participants during their stay (in Moldova the meal cost was available in the hospital's accounting reports). The cost of an inpatient stay was calculated in Ethiopia, India and Moldova as the sum of ward staff costs, overhead costs (including all health facility administration costs) and a 'hotel' cost (utilities, bed and meals) and consumables to deliver the RR-TB treatment. In Uganda, we used a fixed cost that included staff costs, overhead costs and the hotel costs. The unit cost per inpatient stay day (consisting of staff costs, overhead and 'hotel' costs) was then multiplied by the number of inpatient stay days collected as part of the trial. The mean inpatient stay duration for each arm and country is shown in Table S7. There was no trial requirement in terms of hospitalisation, so site clinicians decided if and for how long participants need to be hospitalised.

In calculating total provider costs, we did not include staff training costs because we did not have access to these data in Ethiopia, India and Moldova. In Uganda, the staff training costs were paid for by the Global Fund and were not included in the analysis for consistency.

Moreover, we only considered overhead costs for the inpatient stay duration.

We were concerned that costs associated with other SAE's (e.g. road traffic accident) would skew the results and to avoid this we costed only SAEs that were assessed to have been caused by the RR-TB or its treatment rather than all SAE's. SAE causality was independently assessed by two clinicians (SBS and SM) blinded to the treatment allocation. They reviewed and coded SAEs based on a decision tree developed for this purpose (figure 1). For each of the 16 SAEs identified this way, the focal health economists checked the clinical trial records and discussed with the treating clinician to collect resource use: staff time, tests, inpatient stays and medication received. Each SAE was

then costed by populating a Microsoft Excel tool developed by the central team (table S8). SAE costing was then added to the total health system costs.

We also included social support costs in the total provider costs, assuming that all patients who were eligible to receive it have claimed it. In India and Uganda social support was provided only during outpatient-based care, while in Ethiopia and Moldova this was given regardless of the hospitalisation status. The social support was paid for by the government in each country and was given as a fixed amount in the form of cash transfer to cover the patients' travel costs to and from the health facility and to help with the food costs. Additional support, such as housing support was available in certain countries for a small proportion of patients, but this was not included in the analysis as it was not representative for a typical pathway.

5.2 PARTICIPANT COSTING

Through the participant cost questionnaire, participants reported data on direct costs (food, transport, medical fees) and income for themselves and their supporters from week 12 until week 76. These consisted of costs for attending directly observed treatment (DOT), scheduled assessment visits and unscheduled assessment visits (for an adverse event for example) made during the interval since the previous interview. Participants were also asked about the number of DOT and unscheduled visits made since the last interview. This questionnaire also contained questions on coping strategies used, such as loans taken, or assets sold as a result of the disease or its treatment.

A separate questionnaire was administered at baseline only and collected information on the pre-disease socioeconomic characteristics of participants, such as employment status, income, number of hours worked, assets owned and housing characteristics. An adapted version of this questionnaire was then administered every 12 weeks until week 76 of follow-up.

The DOT and unscheduled assessment visits costs were calculated by multiplying the costs incurred by the number of visits, as revealed by each participant. In calculating scheduled assessment visit costs, we assumed that each participant followed the trial assessment schedule (table S9) and then multiplied this number by the total assessment visit costs as revealed in the participant costs questionnaire. Total direct cost per participant was estimated using the formula below:

$$\begin{aligned} \text{Totaldirectcost} = \quad & (\text{CostDots} * \text{NoVisitsD}) + \\ & (\text{CostSVisits} * \text{NoVisitsS}) + \\ & (\text{CostUVisit} * \text{NoVisitsU}) + \text{CostSupp} \end{aligned}$$

,where NoVisitsD, NoVisitsS, NoVisitsU=number of visits for attending DOTs, scheduled and unscheduled visits, respectively

In Uganda, participants on the Oral regimen reported 12 additional minutes of transport time compared to Control. This was not related to treatment allocation but to the extension of the catchment area, which led, by chance, to more participants on the Oral regimen living further from the hospital, compared to Control. We therefore adjusted for this by using pooled mean transport costs for both Oral and Control. To the transport cost we have then added the food and supporter cost as reported by each trial participant and multiplied by the number of visits.

We used participants' income to calculate catastrophic cost instead of using household income. Collecting total household income would have either required us to obtain consent from all household members, which we considered unfeasible, or to ask trial participants to disclose income of other household members. This would have been potentially difficult or compromising for them and risked inaccuracy. Moreover, income-related questions are highly sensitive, and we did not wish to undermine the health economic data collection. We were also cognisant of the time burden on trial participants which is already high for completion of the patient costing questionnaires.

5.3 HEALTH-RELATED QUALITY-OF-LIFE DATA ESTIMATION

Health-related quality-of-life data (HRQoL) were collected using the EQ-5D-5L form, at 7 interview time points: week 0, then every 12 weeks until week 60 and then at week 76.

The value sets were used to calculate the QALY using the formula below and annualised accordingly:

$$\text{QALY} = \sum \left[\frac{(U_i + U_{i+1})}{2} \right] \times (t_{i+1} - t_i)$$

, where U= utility value and t=time period between interviews

Although an Indian value exists[5] we did not use this to calculate QALYs as this was not published on the EuroQoL website as a valid value set at the time of the analysis.

5.4 EFFICACY OUTCOMES

We used pooled efficacy outcomes from all STREAM countries (Ethiopia, India, Moldova, Uganda, Georgia, South Africa and Mongolia) as the main outcome for the CEA. This is because the pooled sample (rather than individual country samples) was powered to show the non-inferiority of the Oral regimen to the Control regimen. It was justifiable to pool efficacy (but not costs) data as they were much more likely to be consistent across countries and less affected by context than costs (wage differentials, patient management strategies, etc.), while also being the closest estimate of the true clinical efficacy under implementation conditions.

5.5 ANALYSIS

We calculated the incremental cost-effectiveness ratio (ICER) for both the cost-utility analysis (CUA) and CEA using the formula below:

$$ICER = \frac{(CostOral - CostControl)}{(MeanEffectOral - MeanEffectControl)}$$

When calculating the ICERs two perspectives have been adopted: provider and societal. For the provider perspective, the difference in health system costs between the Oral and Control were calculated and then divided by the difference in the mean effect (QALYs for the CUA and pooled trial efficacy outcome (favourable/unfavourable) for the CEA in the base case and individual country efficacy outcome for the CEA in the sensitivity analysis).

When a societal perspective was adopted, we divided the difference in societal costs between the Oral and Control by the difference in the mean effect (QALYs for the CUA and the efficacy outcome for the CEA). The ICER for Six-month regimen vs Control was calculated in a similar way, by replacing the cost and effects for the Oral with the costs and effects for the Six-month (table S11).

5.6 DATA QUALITY AND MANAGEMENT

The study team received monthly query reports from the MRC Clinical Trials Unit, UCL central team that were then corrected by the local health economists. Quality assurance exercises were carried out during the trial, in two stages. First, during site visits, when the central health economic team randomly reviewed completed patient CRFs for logic and consistency and cross-checked these with the data already inserted into the database. These checks took place, on average, every six months at each site. Second, by randomly reviewing answers inserted into the database; this was done every two months. Where checks identified discrepancies or missing responses to certain questions, we cross-checked all CRFs for that site. The queries were then resolved by the study team and corrections made by discussing with the interviewing nurse and the participants.

5.7 HANDLING MISSING DATA

We imputed responses for two categories: for those who withdrew consent and for the missing visits. Three participants withdrew consent in India at different trial stages- two on the Control regimen and one in the Oral regimen. There were 9 missed visits in Ethiopia: five in the Control regimen, two in the Oral regimen and four in the

Six-month regimen. One patient died in Moldova (on Control arm), three in Uganda (one in Control, two in the Oral arm), and one in India (the Oral arm). For those patients who died during follow-up we assumed their costs to be zero from the point of death. Multiple imputation was conducted using predictive mean matching (PMM), chained multiple imputations[6]. Under the missing at random assumption, we imputed responses on transport and food cost spend for attending DOT, assessment visits and unscheduled assessments, guardian costs, lost income and supplementary food expenditure. Variables included in the imputation models were age at trial enrolment, sex, weight, HIV status and visit week. Mean participant cost per visit was then calculated using Rubin's rules.

The missing responses to the EQ-5D-5L questionnaire were also imputed. Beside the baseline characteristics, the previously reported values (imputed or not) were also included in the imputation model.

6.0 SENSITIVITY ANALYSES

We varied the bedaquiline cost per 200mg pill from $1.8 to $1.0 in a stepwise manner to see if the results were robust to this. The health system costs with the varied bedaquiline pricing are in table S10.

The ICERs and results for the base case and sensitivity analyses conducted can be seen in table S11.

7.0 TIME HORIZON

We collected health economic data in four out of seven trial countries where, by chance, no participants on the Control arm reported hearing loss as an SAE, although several (18 (9%) in Control vs. 4 (2%) in Oral regimen) have been reported in STREAM2 countries where the health economic analysis was not conducted[21]. This could have had a minor impact on CUA results (i.e. through QALYs and provider costs), though not on the CEA, where we used pooled clinical trial outcomes that captured participants who suffered hearing loss. Using a simple Markov model, we estimated the lifetime effect of hearing loss on QALYs. Participants who had active RR-TB entered the model at 34 years old (the mean age of participants enrolled in the health economic component) and exited at 85 years old. Therefore, there were 52 model cycles. Patients had the possibility of being in three states, hearing loss, no hearing loss or death. Once in the hearing loss or no hearing loss state, it was assumed that participants can only move to the death state. It was assumed that participants who experience hearing loss will have the QALYs a quarter lower than the mean QALYs for the participants who do not have hearing loss issues, for each arm.[7] It is well documented that people who had TB during their lifetime have higher mortality rates than those people who had no TB. We therefore used mortality rates for post-TB patients for the whole cohort (table S12).[8] A 3% discount rate was used for future QALYs.

The modelling showed that the Oral regimen would result in an additional 0.009 QALYs per year and would not change our base case findings. In terms of costs, the hearing loss SAE cost the health provider $494 (for the one participant from the Six-month regimen that had severe hearing loss in our sample), including bilateral hearing aids, resulting in an additional $10·10 in per patient provider costs for the Six-month regimen. Using this figure and the trial's percentage difference in hearing loss of Control vs Oral (7%), managing hearing loss would cost health providers an additional $34·60 overall and would not change our findings. However, this is a crude estimate based on a single case and does not capture the wider effects of hearing loss on HRQoL or ability to work. An analysis of these wider effects is beyond the scope of this paper.

Income loss, the largest component of participant costs, was linked to inpatient stay duration which varied between trial sites, with the longest mean duration being the 18.4 weeks (129 days) recorded in Moldova (table S7). Thus, the major driver of participant costs was captured through measurement of income loss to week 76 of follow-up. It would have been difficult to estimate this beyond the week 76 (as some people recover financially, while some are caught in a poverty trap).

8.0 SUPPLEMENTARY RESULTS

COVID19 lockdowns began during the data collection period and participant questionnaires were completed via telephone until the lockdowns ended, when face-to-face interviews resumed. By the time COVID was declared a pandemic in March 2020, 111 participants (42/111 control, 41/111 oral, 28/111 six-month) had their treatment and follow-up completed, while 189 were still under treatment or follow-up (73/189 control, 76/189 oral, 40/189 six-month). We have not collected data on whether the COVID pandemic or the related lockdowns affected the self-reported income. However, there were no temporal discrepancies for the control and oral regimens in the number of patients enrolled before or after COVID was declared a pandemic, so any changes in income would have affected both arms equally. In the six-month regimen, more patients were under treatment or follow-up in March 2020 when COVID became a pandemic. This could have biased (overestimated) the income loss calculations for those patients who have not returned to work for reasons other than their RR-TB further decreasing TB-related income loss. However, the six-month regimen is already less expensive than control from a societal perspective in both Ethiopia and India, so further decreasing the income loss would only decrease the overall cost and would not change our conclusions.

No amendments were made to the participant cost and socio-economic questionnaires; however, we used the telephone-specific EQ-5D-5L form to collect quality of life data.[9] We used COVID19 diaries at each site, to understand the effects of the COVID lockdowns on our results. This way we found out that some participants stopped attending in-person assessment visits, and this could have resulted in lower transport and food cost for participants across all arms.

Further analysis was conducted to understand what financial coping mechanisms patients employed to fund RR-TB treatment. The results show that, across the Oral and Control arms between 5-10% of participants in Ethiopia had to borrow money or sell assets to fund treatment, 78-79% in India, 0-4% in Moldova and 41-83% in Uganda (figure 2). The most commonly sold assets were land, TV and radio (table S13).

We have also compared the three regimens tested in STREAM in Ethiopia and India only, where we had enough data to make the comparison.

In the CUA, in both Ethiopia and India, the Oral regimen was strongly dominated, from both a provider and societal perspective, as it had higher costs and lower QALYs and it was eliminated from the comparison. The remaining Six-month vs. Control comparison is presented in the paper.

In the CEA, the Six-month regimen dominates both the Oral and Control regimen, from both a provider and societal perspective, as it results in lower provider/societal costs and better clinical outcomes, in both Ethiopia and India.

The percentage of participants who experienced catastrophic costs using different threshold values can be seen in table S14. Over 53% of trial participants reported being the primary income earner of the household.

Costs that were necessary for monitoring of both oral and injectable-containing regimens accounted for the majority of monitoring costs (table S2). Eliminating the costs that could be judged necessary only for monitoring the injectable-containing regimen would result in savings of approximately $73.6 in India (4%), $63.5 in India (10%), $103.7 in Moldova (22%) Moldova and $247.3 (12%) in Uganda out of total monitoring costs, compared to Control and does not change estimates of cost-effectiveness.

9.0 PROTOCOL DEVIATIONS

Economic evaluation was conducted in line with the protocol[10] apart from the following deviations.

The number of missing data was low overall, so we have not conducted average, lowest and highest point imputations for the missing data as initially planned. We have, however, conducted multiple imputation and complete case analysis.

We have not calculated net monetary benefit (NMB) as this is heavily reliant on a WTP threshold value. The countries where the cost-effectiveness analyses were conducted do not have a pre-set threshold value and the use of one to three times gross domestic product per capita threshold is not considered appropriate.[11,12] We therefore decided not to use the threshold as a decision rule and instead we presented the results using cost-effectiveness acceptability curves (CEACs) as a best-practice alternative.

Also, we have not used an additional questionnaire to explore how COVID impacted participants' income, spending, or health-related quality of life. We have instead collected qualitative data to explore this and the results will be reported separately.

Patients were asked whether they had a guardian during treatment and whether this guardian lost an income when accompanying the participant to get their treatment. Their lost time was assumed to equal the patient's and assumed to be equivalent to the participant's income loss. This is in contrast with the protocol where guardian's time was suggested to be valued at the national minimum wage. National minimum wage does not exist in most countries we conducted the study in and would not accurately reflect the losses of those who earn higher than this in countries where such an income exists. ^

^This paragraph was only included in the PhD thesis and not included in the published version of the appendix.

10.0 SUPPLEMENTARY TABLES AND FIGURES

Table S1 Consolidated Health Economic Reporting Standard checklist

Topic	No.	Item	Location where item is reported
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title is: Within-trial economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin resistant tuberculosis in STREAM Stage 2
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	At the start of the paper, on page 1-2
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Covered in the Introduction section on page 3
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Health economic analysis plan developed and published in BMJ Open
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Described at the end of the Study design sub-heading on page 3
Setting and location	6	Provide relevant contextual information that may influence findings.	Described under the study design sub-heading on page 3 and section 5 of the supplement
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Described at the beginning of the Study design sub-heading on page 3
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Described at the end of the cost-utility and cost-effectiveness analyses sub-heading on page 5
Time horizon	9	State the time horizon for the study and why appropriate.	Described at the beginning of the Study design sub-heading on page 3
Discount rate	10	Report the discount rate(s) and reason chosen.	Section 4 of the supplement
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Described under HRQoL and Efficacy outcome sub-headings on page 4
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Efficacy outcome described under Efficacy outcome sub-heading on page 4

			Utility weights have been collected using EQ-5D-DL as described under the HRQoL sub-heading on page 4
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Described under the cost-utility and cost-effectiveness analyses on page 5 of the manuscript and under section 5.3 in the supplement
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Described under the participant costs and provider costs sub-headings on page 3
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Reported under Analysis sub-heading on page 4 and section 5 of the supplement
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	A Markov model was used to estimate the lifetime effect of hearing loss on QALYs. Patients had the possibility of being in three states: hearing loss, no hearing loss, or death. Once in the hearing loss or no hearing loss state, it was assumed that participants can move to the death state (as modelling starts 60 weeks after injectable treatment was stopped). Model can be seen in Figure S3.^
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	N/A as not a model-based evaluation
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Randomised trial design as described under study design sub-heading on page 3
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Described under sensitivity and statistical analyses sub-heading on page 5
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Described under sensitivity and statistical analyses sub-heading on page 5
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Described in the protocol under patient and public involvement sub-heading
Results			

Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Tables S2- S7 in the supplement
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Tables 2 and 3 and also described under participant costs, provider costs and HRQoL outcomes sub-headings on pages 5-6
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Described under sensitivity analyses sub-heading on pages 7-8 and figures 1 and 2
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Described in the protocol under patient and public involvement sub-heading
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Reported under discussions section on pages 8-10
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Described under role of the funding source heading on page 6
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	ICMJE forms completed by all co-authors

337 ^ Indicates that this section has been revised as part of the PhD thesis and not included in the published version of
338 the appendix.

339 **Table S2 Mean provider costs and incremental costs by cost category and treatment phase for Control, Oral and Six-month regimen by country**

Country	Resource Element	Control			Oral			Six-month			Incremental cost (cost difference between intervention and control)	
		Intensive phase (US$)	Continuation phase (US$)	Total (US$) (%)	Intensive phase (US$)	Continuation phase (US$)	Total (US$) (%)	Intensive phase (US$)	Continuation phase (US$)	Total (US$) (%)	Control minus Oral (US$)	Control minus Six-month (US$)
Ethiopia	Inpatient stay	359·8	0·0	***359·8 (12·7)***	461·1	15·1	***476·2 (14·1)***	372·7	39·7	***412·4 (16·2)***	116·4	52·6
	*Monitoring tests	801·3	1039·4	***1840·7 (64·8)***	801·3	1039·4	***1840·7 (54·5)***	380·2	916·2	***1296·3 (50·9)***	0·0	-544·4
	Regimen medication^	241·4	206·9	***448·3 (15·8)***	370·8	460·8	***831·6 (24·6)***	254·1	436·0	***690·1 (27·1)***	383·3	241·8
	Outpatient visits	39·1	42·5	***81·6 (2·9)***	22·5	35·3	***47·8 (1·4)***	15.3	29·6	***44·9 (1·76)***	-33·8	-36·7
	Social support	36·6	73·0	***109·6 (3·9)***	28·6	72·4	***101·0 (3·0)***	36·5	68·7	***105·2 (4·1)***	-8·6	-4·4
	Serious Adverse Events	0·0	0·0	***0 (0·0)***	46·7	24·1	***70·8 (2·1)***	0·0	0·0	***0 (0·0)***	70·8	0·0
	Total regimen costs (% of total)	**1478·2 (52)**	**1361·8 (48)**	**2840·0**	**1731·0 (51)**	**1647·1 (49)**	**3378·1**	**1058·7 (42)**	**1490·2 (58)**	**2549·0**	**538·1**	**-291·0**
India	Inpatient stay	132·7	0·0	***132·7 (9·2)***	100·6	0·0	***100·6 (6·3)***	101·7	0·0	***101·7 (7·2)***	-32·1	31·0
	*Monitoring tests	291·6	344·1	***635·7 (44·2)***	291·6	344·1	***635·7 (39·5)***	136·9	310·7	***447·6 (31·8)***	0·0	188·1
	Regimen medication^	253·4	213·9	***467·3 (32·5)***	319·2	386·3	***705·5 (43·9)***	223·9	452·4	***676·3 (48·0)***	238·2	-209·0
	Outpatient visits	58·5	54·2	***112·7 (7·9)***	54·3	50·2	***104·5 (6·4)***	40·3	45·6	***85·9 (6·2)***	8·2	26·8
	Social support	24·7	37·1	***61·8 (4·3)***	24·7	37·1	***61·8 (3·8)***	12·4	33·6	***46·0 (3·3)***	0·0	15·8
	Serious Adverse Events	8·6	3·3	***11·9 (1·9)***	18·5	1·4	***19·9 (0·0)***	6·6	10·3	***16·9 (3·6)***	-8·0	-5·0
	Total regimen costs (% of total)	**769·5 (54)**	**652·6 (46)**	**1422·1**	**808·9 (50)**	**819·1 (50)**	**1628·0**	**521·8 (38)**	**852·6 (62)**	**1374·4**	**-205·9**	**47·7**
Moldova	Inpatient stay	1271·5	399·2	***1670·7 (53·4)***	1249·0	314·1	***1563·1 (46·5)***	N/A	N/A	N/A	-107·6	N/A
	*Monitoring tests	207·4	264·3	***471·7 (15·1)***	207·4	264·3	***471·7 (14·0)***	N/A	N/A	N/A	0·0	N/A
	Regimen medication^	276·0	212·4	***488·4 (15·6)***	376·8	459·9	***836·7 (24·9)***	N/A	N/A	N/A	348·3	N/A

	Outpatient visits	92·4	60·2	***152·6 (4·9)***	104·1	60·2	***140·1 (4·9)***	N/A	N/A	N/A	12·5	N/A
	Social support	28·3	282·4	***310·7 (9·9)***	31·2	295·9	***327·1 (9·7)***	N/A	N/A	N/A	16·4	N/A
	Serious Adverse Events	34·8	0·0	***34·8 (1·2)***	0·0	0·0	***0 (0·0)***	N/A	N/A	N/A	-34·8	N/A
	Total regimen costs (% of total)	**1910·4 (61)**	**1218·5 (39)**	**3128·9**	**1968·5 (59)**	**1394·4 (41)**	**3362·9**	N/A	N/A	N/A	**234·0**	N/A
Uganda	Inpatient stay	722·9	0·0	***722·9 (15·3)***	1024·1	0·0	***1024·1 (18·8)***	N/A	N/A	N/A	301·2	N/A
	*Monitoring tests	1039·3	1021·2	***2060·5 (43·7)***	1039·3	1021·2	***2060·5 (37·9)***	N/A	N/A	N/A	0·0	N/A
	Regimen medication^	217·4	198·8	***416·2 (8·8)***	359·0	453·2	***812·2 (14·9)***	N/A	N/A	N/A	396·0	N/A
	Outpatient visits	107·1	91·7	***198·8 (4·2)***	59·1	91·7	***150·8 (2·8)***	N/A	N/A	N/A	48·0	N/A
	Social support	514·5	771·7	***1286·2 (27·3)***	514·5	771·7	***1286·2 (23·7)***	N/A	N/A	N/A	0·0	N/A
	Serious Adverse Events	12·7	15·2	***27·9 (0·6)***	56·2	47·9	***104·1 (1·9)***	N/A	N/A	N/A	75·3	N/A
	Total regimen costs (% of total)	**2613·9 (55)**	**2098·6(45)**	**4712·5**	**3052·2 (56)**	**2385· (44)**	**5437·9**	N/A	N/A	N/A	**725·4**	N/A

Mean bedaquiline cost per treatment course was $494 in Ethiopia, $427 in India, $495 in Moldova and $481 in Uganda. Out of total provider costs, this accounted for 15% in Ethiopia, 26% in India, 15% in Moldova and 9% in Uganda.

Table S3 Consumables and staff unit costs and their sources for Ethiopia (E), India (I), Moldova (M) and Uganda (U)

Drug type/ Type of test	Estimated unit cost (US$, 2021)				Source of unit cost			
	E	I	M	U	E	I	M	U
N-95 mask (per unit)	1·6	2·1	1	1·3	Private pharmacy	Government e-market	IMSP Financial report	Joint Medical Stores
Surgical mask (per unit)	0·1	0·1	0·03	0·04	Private pharmacy	Government e-market	IMSP Financial report	Joint Medical Stores
Gloves (per unit)	0·3	0·3	0·1	0·03	Private pharmacy	Government e-market	IMSP Financial report	Joint Medical Stores
Syringe 5cc (per unit)	0·1	0·3	0·03	0·04	Private pharmacy	Government e-market	IMSP Financial report	Sinoafrica medicines and health ltd
Alcohol 1000ml (per unit)	2·8	1.0	5·2	8·4	Private pharmacy	Government e-market	IMSP Financial report	Joint Medical Stores
Medical patch (per unit)	0·05	0·03	0·04	0·02	Private pharmacy	State Drug Store, Programmatic management of drug-resistant TB- Central TB Division	IMSP Financial report	Joint Medical Stores
Food menu for inpatient stays per day (per item)	3·1	1·5	2·2	NA	Own estimation based on current market price; based on a weekly food menu prepared for MDR/RR-TB patients at AHRI Hospital	N/A	N/A	N/A
Inpatient cost per night (per item)	4·23	11·2	12·9	22·4	AHRI Hospital	Tambaram Sanatorium dietician department and own calculations	Financial report for the National Health Insurance System	Mulago hospital complex
Clinician cost (per minute)	0·02	0·1	2·1	0·08	Ethiopian government salary scale for health professionals; mid-point	Staff salary of Tambaram TB Hospital; mid-point	Moldovan government salary scale for health professionals; mid-point	Mulago Hospital TB unit
Nurse cost (per minute)	0·01	0·05	1·3	0·06	Ethiopian government salary scale for health professionals; mid-point	Staff salary of Tambaram TB Hospital; mid-point	Moldovan government salary scale for health professionals; mid-point	Mulago Hospital TB unit
Psychiatrist cost (per minute)	0·02	0·03	1·1	0·06	Ethiopian government salary scale for health professionals; mid-point	Staff salary of Tambaram TB Hospital; mid-point	Moldovan government salary scale for health professionals; mid-point	Mulago Hospital TB unit

Table S4 Tuberculosis drugs unit costs used in the analysis

TB drugs	Estimated unit cost (US$, 2021) per tablet/vial
Kanamycin 1g vial	0·99~
Isoniazid 300mg	0·02
Prothionamide 250mg	0·09
Moxifloxacin 400mg	0·16
Levofloxacin 250mg	0·05
Pyrazinamide 400mg	0·02
Clofazimine 100mg	0·81
Ethambutol 400mg	0·04
Linezolid 600mg	0·39
Cycloserine 250mg	0·26~
Capreomycin 1g	2·53
Bedaquiline 100mg	1·81

If a price range was provided we cautiously used the highest value, in accordance with the GDF recommendations for budget planning

~ Unit costs were not available in the 2021 GDF Medicine Catalogue, but in the 2018 one. Unit prices thus have been inflated to 2021 prices.

Table S5 Laboratory tests by country (Unit costs $)

Country	Type of test/panel	Unit cost ($)	Source
Ethiopia	Haematology panel (Red Blood Cell count [RBC], White Blood Cell count [WBC], Platelets, Haemoglobin, Haematocrit, MCV, MHC)	3·3	International Clinical Laboratory
	Sodium, Serum Bicarbonate, Calcium, Serum Potassium, Magnesium, Chloride, Blood Glucose, **Blood Urea Nitrogen, Serum creatinine**, Alkaline phosphatase, Pancreatic amylase, Human serum albumin, Total protein, AST, ALT, Total Cholesterol, Creatine phosphokinase, Gammaglutamyltransferase, Creatine phosphokinase of muscle / brain, Total direct-indirect bilirubin, Triglycerides, Lipase, Lactate Dehydrogenase, Uric Acid)	17·3	International Clinical Laboratory
India	LFT&RFT profile (RBC, WBC, Platelets, Hb level, Hematocrit, MCV, MCH, **Sodium, Serum Bicarbonate, Serum Potassium, Chloride**, Blood Glucose, **Blood Urea Nitrogen, Serum creatinine**, Alkaline phosphatase, Human serum albumin, Total protein, AST, ALT, Total direct-indirect bilirubin, Triglycerides, Uric acid)	9·4	Hi-tech Diagnostic centre
	Calcium (corrected for albumin)	1·6	Hi-tech Diagnostic centre
	Magnesium	1·6	Hi-tech Diagnostic centre
	Pancreatic amylase	4·7	Hi-tech Diagnostic centre
	Total cholesterol	2·0	Hi-tech Diagnostic centre
	Creatine phosphokinase	3·2	Hi-tech Diagnostic centre
	Gammaglutamyltransferase	5·6	Thyrocare laboratories limited
	Creatine phosphokinase of muscle/ brain	3·0	Thyrocare laboratories limited
	Lipase	4·0	Hi-tech Diagnostic centre
	Lactate Dehydrogenase	5·4	Hi-tech Diagnostic centre
Moldova	Hematology panel (RBC, WBC, Platelets, Haemoglobin, Haematocrit, MCV, MCH)	4·5	Government decision on tariffs for medical services
	Sodium	1·2	
	Serum bicarbonate	1·6	
	Calcium (corrected for albumin)	0·0	
	Serum Potassium	1·2	
	Magnesium	1·2	
	Chloride	1·1	
	Blood Glucose	1·0	
	Blood Urea Nitrogen	1·1	
	Serum creatinine	1·0	
	Alkaline phosphatase	1·1	
	Pancreatic amylase	1·9	
	Human serum albumin	1·1	
	Total protein	1·2	
	AST	1·1	
	ALT	1·1	
	Total cholesterol	1·1	
	Creatine phosphokinase	1·3	
	Gammaglutamyltransferase	1·1	
	Creatine phosphokinase of muscle brain	1·4	

	Total direct-indirect bilirubin	1·1	
	Triglycerides	1·1	
	Lipase	2·4	
	Lactate Dehydrogenase	1·3	
	Uric Acid	1·2	
Uganda	Blood glucose	2·8	Private laboratories in Mulago hospital complex
	CBC (Complete/ full blood count)	4·2	
	LFT profile (AST, ALT, alp, T·bil, D.bil, alb, GGT, T.protein)	15·4	
	RFT profile (Creatinine, Urea, Sodium, Chloride, Serum Potassium)	12·6	
	Magnesium	2·8	
	Calcium (corrected for albumin)	4·8	
	Pancreatic amylase	7·0	
	Total cholesterol	4·2	
	Triglycerides	4·2	
	Lipase	4·2	
	Lactate dehydrogenase	4·2	
	Serum bicarbonate	5·6	
	Uric acid	4·2	
	CK-MB	5·6	
	Creatine phosphokinase	4·2	

Tests highlighted in **bold** are monitoring tests for renal toxicity, usually used for the injectable-containing regimens.

Table S6 Further test unit costs and their sources for Ethiopia (E), India (I), Moldova (M), Uganda (U)

	Costs (US$)				Sources			
Type of test	**E**	**I**	**M**	**U**	**E**	**I**	**M**	**U**
Visual acuity	6·4	1·3	1·9	0·1	St. Paulos Hospital	Hi Tech Diagnostic Centre	Government Decision on Tariffs for Medical Services	Visual acuity chart cost, STREAM financial records
Colour vision test	1·1	1·1	0·8	0·1	AHRI Hospital			
Hearing test (audiometry)	2·1	3·8	3·1	8·4	AHRI Hospital			Private laboratories in Mulago hospital complex
Urinalysis	2·2	0·9	2·4	2·2	International Clinic Laboratory			
ECG	2·7	1·6	2·9	14.0	St. Paulos Hospital			
Sputum smear	7·4	2·5	2·5	5·6	International Clinical Laboratory			
Sputum culture	7·2	5·8	24·9	16·6	International Clinical Laboratory			
TSH& thyroxine of free thyroxine	5·7	5·6	5·2	14.0	International Clinic Laboratory			
Chest x-ray	7·4	2.0	9·6	8·4	International Clinical Laboratory			

Table S7 Mean inpatient stay duration (days) by country and arm from participant records

Regimen/Site	Ethiopia	India	Moldova	Uganda	Mean
Control	44·0	13·0	129·0	32·0	54·5
Oral	58·0	9·0	121·0	48·0	59·0
Six-month	50·0	10·0	N/A	N/A	30·0
Mean	50·7	10·7	125·0	40·0	

Table S8 Individually costed Serious adverse events by main cost category and treatment regimen

Country	Serious adverse event	Cost categories (US$ 2021)				Unit cost per serious adverse event ($)	Arm	Mean cost per patient
		Drug costs	Test costs~	Staff costs	Hospitalisation costs			
Ethiopia	Vomiting	208·0	129·0	28·6	115·7	481·3	Oral	24·1
	Left hydro-pneumothorax	298·4	79·8	166·2	388·8	933·2	Oral	46·7
India	Hypotension	29·3	26·8	19·3	74·4	149·8	Six-month	3·1
	Pneumothorax	0·0	19·2	26·7	124·0	169·9	Six-month	3·5
	Vomiting	19·2	2·5	1·0	44·8	67·5	Oral	1·4
	Vomiting	40·6	5·5	47·5	795·2	888·8	Oral	18·5
	Breathlessness	39·9	86·8	20·0	111·6	258·3	Control	5·6
	Generalized Weakness	59·3	0·0	14·9	62·0	136·2	Control	3·0
	Hospitalization with Breathlessness	9·7	0·0	8·0	37·2	54·9	Control	1·2
	Hospitalization due to Breathlessness	68·8	0·0	5·0	24·8	98·6	Control	2·1
	Hardness of hearing (bilateral)	0·0	448·6	45·6	0·0	494·2	Six-month	10·3
Moldova	Toxic Hepatitis	676·8	103·1	90·3	0·0	870·2	Control	34·8
Uganda	Unknown, possibly an arrhythmia	0·0	75·6	2·0	201·6	279·2	Control	12·7
	Empyema Thoracis	0·9	143·3	339·7	1702·4	2186·3	Oral	91·1
	Respiratory failure	0·0	19·6	2·0	291·2	312·8	Oral	13·0
	Pulmonary Tuberculosis	0·0	65·0	68·8	201·6	335·4	Control	15·2

Mean SAE cost per patient was calculated by dividing the measured SAE cost by the number of participants enrolled in that specific arm and country.

~Test costs include consumables costs

Table S9 Assessment schedule for all patients recruited in STREAM2. Extract from the trial protocol

The following assessment schedule applies to *all* treatment arms in the STREAM trial as soon as Stage 2 begins (for sites participating in Stage 2).

Observation/Investigation	Screening	Randomisation	Treatment Phase			Post-Treatment Phase
			Intensive Phase		Continuation Phase	Follow-up
			Weeks 1 – 3	Weeks 4 onwards		
Written informed consent	X	X				
Demographics	X	X				
Medical History	X	X				
Alcohol Use Questionnaire		X		Week 16	Week 32	Week 52
Clinical Examination	X	X	X	X	X	X
Clinical assessment (including AEs and concomitant medication during treatment)	X	X	X	X	X	X
Height		X				
Weight	X	X	X	X	X	X
Visual acuity and colour tests		X		Week 12 (and if symptoms)	Week 28 and 40 (and if symptoms)	
Hearing test	X		Week 1 (If clinically indicated)	Week 4, 8 and 16	At the start of the continuation phase[11], Week 28 and 40	Weeks 52, 76 and 132
Haemoglobin		X				
HIV antibody test	X					Week 76[15]
CD4 (in HIV positive patients)	X		According to national guidelines, at end of BDQ dosing and at end of study			
Viral load (in HIV positive patients)	X			X[13]	X[13]	X[13]
Hepatitis A, B and C testing		X				
Urinalysis (sample sent to) central lab		X	X	X	X	X[17]
Urine: HCG Pregnancy test	X	X	If clinically indicated, at end of BDQ dosing and at end of study			
Chest X-ray[14]	X					
ECG (12-Lead)[3]	X	X	X	X	X	X
Additional Post-Dose ECG (12 Lead) for sites in PK study[4]			Week 2	Weeks 12	Weeks 24 & 40	
Sputum smear and culture[2]	X[1]	X[1]		X[1]	X[1]	X[1]
Sputum for drug resistance testing	X[6]					
Patient's costs (in selected sites)		X		X[12]	X[12]	X[12]
Blood sample for storage (if consents)[5]		X[5]			X[5]	
PK samples[7,8,9]		X	Week 2	Weeks 4, 12	Weeks 24& 40	Weeks 76, 120 & 132
Laboratory safety tests[10]	X	X		X	X	X[16]

TSH & thyroxine of free thyroxine	X					Weeks 40 and 76

X indicates assessments required at particular visits

[1] At screening and randomisation two samples will be collected, with an additional third early morning sample if possible. Two samples will be collected at each subsequent visit, ideally one early morning and one spot sample, or two spot samples if the patient does not provide an early morning sample. Refer to the STREAM Microbiology Manual for details of the tests to be undertaken.

[2] Screening, randomisation, and all positive isolates of MTB post-randomisation from week 8 onwards will be shipped to the reference laboratory for full drug susceptibility testing.

[3] An ECG will be conducted prior to randomisation, a further ECG will then be conducted 4 hours after administering treatment at the randomisation visit. 12-lead ECG will then be collected at each visit until Week 76. In participants who at Week 76 have QTcF increases from baseline, single 12-lead ECGs will be collected at each visit until the QTcF returns to less than a 10ms increase above the baseline value. Single ECGs will be collected; however for QTcF prolongatons of more than or equal to 500 ms, two further ECGs must be collected.[4] For patients on arms C and D, enrolled at sites that have been pre-selected for the PK sub-study, an additional 12-lead ECG will also be conducted 4 hours after administering treatment at the week 2, 12, 24 and 40 visits

[5] A blood sample will be collected for storage at randomisation and week 16 , for patients consenting/assenting to sample storage.

[6] Sputum will be collected for drug sensitivity testing for resistance to rifampicin, fluoroquinolones and second-line injectables. If LPA results for fluoroquinolones and second-line injectables sensitivity are inconclusive, then these tests need to be repeated on a new sputum sample before randomisation.

[7] The PK samples will be collected pre-dose and post-dose (sample from Week 2 visit). Details of PK sampling are specified in section 8.2.1.

[8] Samples for analysis of the plasma concentration of nevirapine (NVP) and lopinavir (LPV)/ritonavir(RTV) must be taken before intake of ARV and study drug. An additional pre-dose sample will be collected if the antiretroviral treatment regimen of a patient is changed, followed by sampling at time points indicated in the Assessment Schedule.

[9] Sample for analysis of the plasma concentration of nevirapine (NVP) and lopinavir (LPV)/ritonavir (RTV) and 4 β OH-cholesterol.

[10] See Section 8.2 for blood test details.

[11] Hearing test will be conducted at the first visit of the continuation phase.

[12] Patient costs collected every 12 weeks from after randomisation in selected sites.

[13] Viral load collected at Week 12, Week 24, Week 40, and Week 76.

[14] A chest X-ray is required at randomisation that is compatible with a diagnosis of pulmonary TB, however if a good quality X-ray is available that was taken in the 4 weeks prior to randomisation it does not need to be repeated

[15] HIV test at week 76 (for patients who were found to be HIV negative at screening). For patients found to be HIV positive at this visit a week 76 viral load measurement should also be taken.

[16] Laboratory safety tests should be undertaken at each visit to Week 76. After Week 76 only if clinically indicated.

[17] Urinalysis to central lab should be undertaken at each visit to Week 76. After Week 76 only if clinically indicated.

Table S10 Health system costing when bedaquiline price was varied in the sensitivity analysis (US$)

Bedaquiline price tested	Oral regimen				Short regimen	
	Ethiopia	India	Moldova	Uganda	Ethiopia	India
1·0	3086·9	1417·1	3150·7	5172·9	2375·0	1185·4
1·1	3114·2	1440·7	3178·1	5199·5	2396·2	1206·8
1·2	3141·5	1464·3	3205·5	5226·1	2417·4	1228·2
1·3	3168·8	1488·0	3232·9	5252·7	2438·5	1249·5
1·4	3196·1	1511·6	3260·2	5279·3	2459·7	1270·9
1·5	3223·4	1535·2	3287·6	5305·9	2480·9	1292·3
1·6	3250·7	1558·8	3315·0	5332·5	2502·1	1313·7
1·7	3278·0	1582·4	3342·4	5359·0	2523·2	1335·0
1·8	3378·1	1628·0	3362·9	5437·9	2549·0	1374·7

Table 10 Cost-utility and cost-effectiveness analysis results (Oral versus Control) for base-case and sensitivity analyses, by country and perspective

Base case/ Sensitivity analysis conducted	Perspective				
		Ethiopia	India	Moldova	Uganda
Cost-utility analysis (CUA)		**Dominant regimen or ICER v WTP threshold*($)**			
Base case	**Provider**	Control dominant	Control dominant	Oral costs more and yields more QALYs ICER vs. WTP: $5965·5 > $2,400, hence Oral unlikely to be cost-effective	Control dominant
	Societal	Control dominant	Control dominant	Oral dominant	Control dominant
Bedaquiline cost	**Provider**	Control dominant	Oral costs less and yields less QALYs ICER vs. WTP $1018·88 < $2,781, hence Oral cost-effective	Oral costs more and yields more QALYs ICER vs. WTP $517·52 < $2,400, hence Oral cost-effective	Control dominant
	Societal	Control dominant	Control dominant	Oral dominant	Oral costs less and yields less QALYs ICER vs. WTP $3,712·3 > $725, hence Oral unlikely to be cost-effective
Complete case	**Societal**	Control dominant	Control dominant	Oral dominant (No missing data)	Control dominant
Retrospectively collected data	**Societal**	N/A	Control dominant	N/A	Control dominant
Cost-effectiveness analysis (CEA)		**Dominant regimen or ICER**			
Base case	**Provider**	4,666·8	1,785·8	2016·5	6,283·6
	Societal	10,398·8	1,681·8	Oral dominant	981·3
Bedaquiline cost	**Provider**	2,141·2	Oral dominant	176·1	3,993·0
	Societal	7,873·2	25·2	Oral dominant	Oral dominant

Complete case	**Societal**	9,260·0	1,569·8	Oral dominant (No missing data)	487·9
Retrospectively collected data	**Societal**	N/A	1,267·6	N/A	1,244·0
In-country efficacy	**Provider**	11,894·6	1,700·0	1368·7	1,521·5
	Societal	26,503·9	1,939·1	Oral dominant	237·6

*****Price decision makers must be willing-to-pay per additional QALY (CUA) or favorable outcome (CEA) to support the introduction of the Oral regimen, with a high (80%) probability that it is cost-effective

Table S12 Death probabilities by age range

Age range	Death probability
18-39	0·0059
40-64	0·0073
>=65	0·0183

Table S13 Assets sold (presented as a negative value)/bought (presented as a positive value) by the participants at between baseline and week 76 of follow up

Assets sold/bought week0 vs. week76, n (%)	Ethiopia			India			Moldova		Uganda	
	Control	Oral	Six-month	Control	Oral	Six-month	Control	Oral	Control	Oral
Mobile phone	0 (0%)	0 (0%)	0 (0%)	4 (9%)	8 (17%)	-1 (-2%)	0 (0%)	-1 (-4%)	2 (9%)	1 (4%)
Refrigerator	1 (5%)	-2 (-10%)	4 (20%)	0 (0%)	1 (2%)	-1 (-2%)	1 (4%)	1 (4%)	-1 (-5%)	1 (4%)
TV	2 (10%)	-1 (-5%)	5 (25%)	5 (11%)	6 (13%)	-3 (-6%)	0 (0%)	0 (0%)	-2 (-9%)	1 (4%)
Radio	3 (14%)	0 (0%)	1 (5%)	2 (4%)	3 (6%)	3 (6%)	0 (0%)	0 (0%)	1 (5%)	4 (17%)
Bicycle	0 (0%)	1 (5%)	0 (0%)	3 (7%)	1 (2%)	1 (2%)	2 (8%)	1 (4%)	0 (0%)	-1 (-4%)
Motorbike	0 (0%)	0 (0%)	0 (0%)	-5 (-11%)	2 (4%)	-2 (-4%)	0 (0%)	0 (0%)	0 (0%)	-1 (-4%)
Livestock	2 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	2 (4%)	0 (0%)	2 (8%)	-2 (-9%)	1 (4%)
Land	1 (5%)	1 (5%)	1 (5%)	5 (11%)	5 (10%)	4 (8%)	0 (0%)	0 (0%)	-1 (-5%)	1 (4%)
Car	0 (0%)	1 (5%)	1 (5%)	-1 (-2%)	1 (2%)	1 (2%)	1 (4%)	1 (4%)	0 (0%)	0 (0%)

Table S1411 Percentage of participants experiencing catastrophic costs using different threshold values

Scenario	Arm or Difference	Ethiopia	India	Moldova	Uganda
Base case 20%	Control	81·0%	88·9%	92·0%	94·7%
	Oral	95·0%	83·3%	96·2%	86·2%
	Control minus oral	-14·0%	5·6%	-4·2%	8·5%
40%	Control	81·0%	73·3%	92·0%	94·7%
	Oral	95·0%	78·6%	96·2%	82·6%

	Control minus oral	-14·1%	-5·2%	-4·2%	12·1%
60%	Control	76·2%	68·9%	84·0%	94·7%
	Oral	80·0%	71·4%	96·2%	78·3%
	Control minus oral	-3·8%	-2·5%	-12·2%	16·5%

Figure S1 Decision tree that was used to assess which SAEs should be included in the health economic component

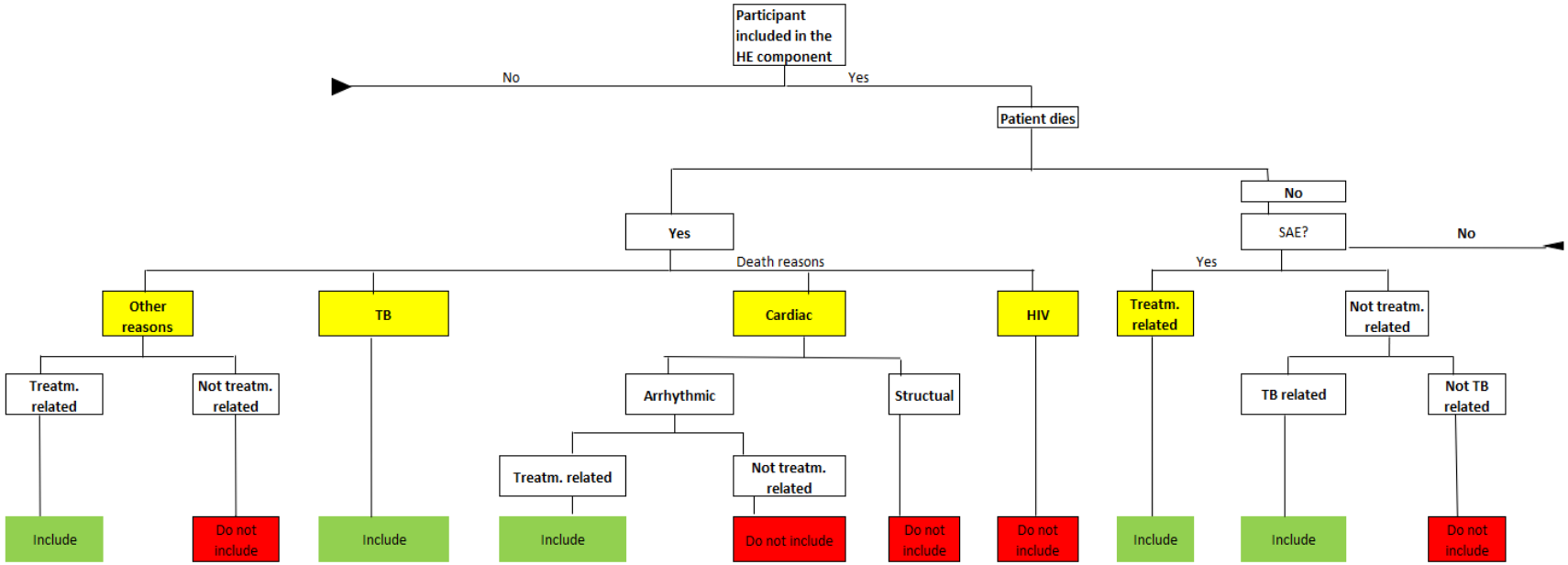


Figure S2. Percentage of patients borrowing money or selling assets to fund TB treatment

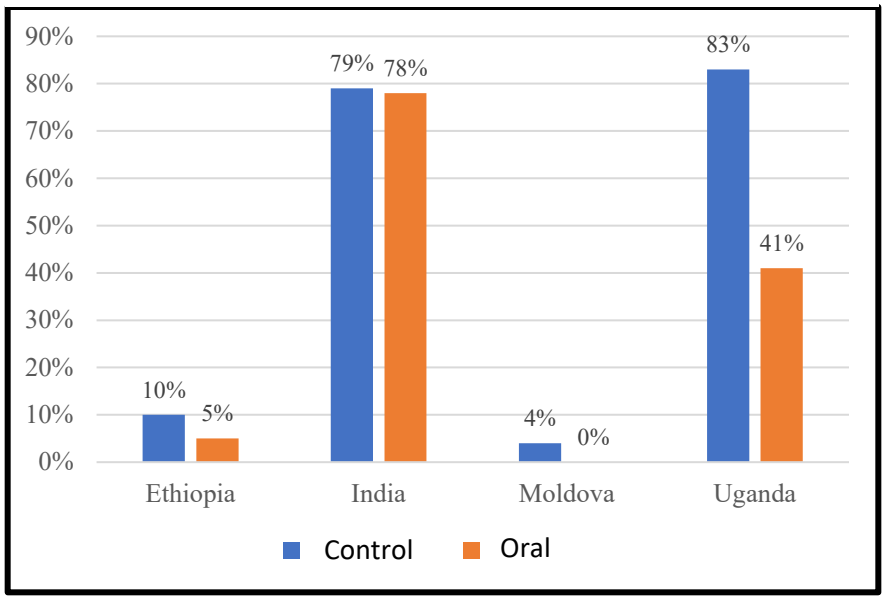
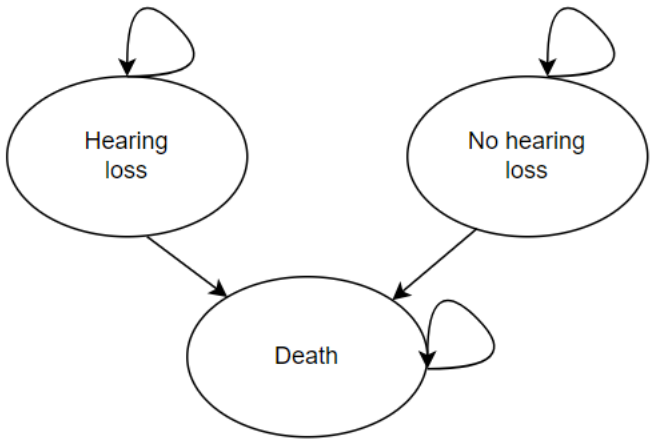


Figure S3^. Markov model used to estimate the lifetime effect of hearing loss on QALYs after 36 weeks after MDR-TB treatment end



^ Indicates that this figure has been included only in the PhD thesis and not included in the published version of the appendix.

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Cost of treatment support for multidrug-resistant tuberculosis using patient-centred approaches in Ethiopia: a model-based method^

^This paper version and the published version differ slightly due to thesis examiner clarification request and because this version did not benefit from journal's proofreading services

Running head: Cost of patient-centred approaches for MDR-TB

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ABSTRACT

Background

Patient and health system costs for treating multidrug-resistant tuberculosis (MDR-TB) remain high even after treatment duration was shortened. Many patients do not finish treatment, contributing to increased transmission and antimicrobial resistance. A restructure of health services, that is more patient-centred has the potential to reduce costs and increase trust and patient satisfaction. The aim of the study is to investigate how costs would change in the delivery of MDR-TB care in Ethiopia under patient-centred and hybrid approaches compared to the current standard-of-care.

Methods

We used published data, collected from 2017 to 2020 as part of the Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) trial, to populate a discrete event simulation (DES) model. The model was developed to represent the key characteristics of patients' clinical pathways following each of the three treatment delivery strategies. To the pathways of 1000 patients generated by the DES model we applied relevant patient cost data derived from the STREAM trial. Costs are calculated for treating patients using a 9-month MDR-TB treatment and are presented in 2021 United States Dollars (USD).

Results

The patient-centred and hybrid strategies are less costly than the standard-of-care, from both a health system (by USD219 for patient-centred and USD276 for the hybrid strategy) and patient perspective when patients do not have a guardian (by USD389 for patient-centred and USD152 for the hybrid

strategy). Changes in indirect costs, staff costs, transport costs, inpatient stay costs or changes in directly-observed-treatment (DOT) frequency or hospitalisation duration for standard-of-care did not change our results.

Conclusion

Our findings show that patient-centred and hybrid strategies for delivering MDR-TB treatment cost less than standard-of-care and provide critical evidence that there is scope for such strategies to be implemented in routine care. These results should be used inform country-level decisions on how MDR-TB is delivered and also the design of future implementation trials.

Keywords: affordability, multidrug-resistant tuberculosis, directly-observed treatment, patient-centred approach, tuberculosis treatment delivery

Background

Globally more people are falling ill with MDR-TB, tuberculosis (TB) which cannot be treated with the two main TB drugs, rifampicin and isoniazid.[1] Health outcomes for MDR-TB patients are considerably worse than for those with drug-susceptible TB. MDR-TB requires longer courses of treatment, which are more costly for both the health system and patients.[1]

In 2021, the MDR-TB incidence rate in Ethiopia was 1.5 per 100,000 population, being one of the 30 high MDR-TB burden countries, as classified by World Health Organization.[1][2] In 2021, 12% of the previously treated cases and 1.1% out of total new cases were MDR-TB. [1] Once diagnosed, treatment requires regular health monitoring and daily medication. In Ethiopia this is provided free of charge for patients, with patients often kept in hospital until they have had two consecutive negative sputum-smear microscopies.

At this point — known as 'conversion' — patients have the option to receive the remainder of their treatment at a health facility, their workplace, or their home. Despite this, in practice, patients often stay in hospital throughout their intensive phase of treatment, which typically lasts 16 weeks and is more drug-intensive; the option to receive DOT at home — or in the workplace — is rarely utilised. For patients receiving care and DOT at the health facility, daily travel to receive medication presents a considerable time and cost burden, particularly considering 78% of Ethiopians live rurally [3], while 84% of MDR-TB centres are in urban locations. [4] Unsurprisingly, the burden of these costs is felt most severely by poorer patients, with higher costs associated with attrition during treatment and poorer health outcomes.[5][6][7] Interviews reveal that many patients consider the frequency of visits 'unnecessary', with some 'begging' for several days' medication at once; despite being outwith the guidelines, healthcare workers admitted to fulfilling these requests.[4]

A trial of a shorter regimen in Bangladesh suggested MDR-TB could be successfully treated with considerably shorter regimens.[8] The STREAM trial investigated the efficacy of this regimen, demonstrating that the 9-month Bangladeshi regimen is non-inferior to the previously recommended 20-to-24-month regimen. In 2017, the 9-month regimen — comprising a 16-weeks Intensive Phase, followed by a 24-weeks Continuation Phase— was adopted as the standard treatment for MDR-TB in Ethiopia.[9] Besides evaluating clinical efficacy, STREAM collected extensive health system and patient-cost data.[10]

While the availability of shorter treatment regimens has provided significant benefits to patients and health systems,[11] patient-costs today remain high, and many patients do not complete treatment, contributing to increased transmission and antimicrobial resistance. [12] Over recent years, across many areas of health, there has been a drive to rethink and restructure health services to increase patient involvement and incorporate their preferences into decisions made on their behalf. Often termed 'patient-centred approach', this model of care factors in patients' personal and social circumstances, has been shown to improve treatment adherence, and leads to better health outcomes, achieved through increased trust and patient satisfaction. [13] While it is clear that adaptations to care-delivery which reduce the demands placed on MDR-TB patients could be greatly beneficial, addressing such issues requires a clear understanding of how programmatic changes would affect patients and the health system.

Using primary data from the STREAM trial and a DES operational model, this study investigates how costs would change in the delivery of MDR-TB care in Ethiopia under new patient-centred approach.

METHODS

Overall approach

We extrapolated data from the STREAM trial to simulate two patient management strategies for MDR-TB compared to the standard of care.

There are two components to the evaluation methodology, a DES model and a cost model. The DES model itself has two parts: (i) the 'model' which uses computer code to represent the key characteristics of patients' clinical pathways, including stochastic elements such as the outcome of a sputum test; (ii) the simulation code which runs the model over time to create treatment pathways for a specified number of patients (1000) for each of the treatment strategies under consideration. The timings spent by patients in each phase of treatment, as revealed by the DES model, are then used in the cost model (by multiplying the timings with the unit costs) to estimate the costs incurred by the health system and by the patient.

This study evaluates two management strategies for MDR-TB in Ethiopia: a patient-centred and a hybrid model, which are each then compared to the current standard-of-care (table 1). The main difference between the standard-of-care, patient-centered, and hybrid models is the location care is provided. The patient-centred strategy sees patients treated as outpatients throughout their treatment, hospitalised only if they experience a serious adverse event (SAE). The nurse delivers medication during these visits (eliminating patient travel to health centres) and once a month collects a sputum sample for testing. DOT home visit duration for nurses was calculated by summing the mean visit duration and mean travel time (for a return journey) as revealed by patients in the STREAM trial which was 45 minutes. The Hybrid strategy sees patients travelling to collect drugs and receive injectable treatment during the intensive phase only, and then follows the patient-centred approach during the less intensive 'continuation phase'. We considered daily DOT visits in the main analysis and tested weekly DOT visits in a scenario analysis.

As in the standard-of-care, both new strategies assume patients who survive an SAE are hospitalised (or kept in hospital if already hospitalised as part of treatment management), receiving their treatment there for the next four weeks.

Discrete event simulation model

The DES model built to incorporate the three strategies, with pathways reflecting patient journeys throughout treatment is summarised in Figure 1.

In the standard-of-care all patients start in hospital. Following conversion they are discharged and receive the remainder of their Intensive Phase treatment as an outpatient with daily trips for DOT and a monthly assessment at hospital. In the patient-centred and hybrid strategies all patients start their treatment as outpatients. After treatment start, the patients who have not died can be in the following treatment states, depending on their allocated strategies: Intensive Phase in hospital, Intensive Phase at home, in hospital with SAE during the Intensive Phase, at home with SAE during the Intensive Phase, in the extended Intensive Phase, in the extended Intensive Phase with SAE, at home in the Continuation Phase or in hospital with SAE during the Continuation Phase.

The likelihoods of SAEs, sputum conversion rates, and death and dropout from STREAM have been amended using a series of assumptions to fit the four-week intervals of the model and can be seen in Table 2.

Cost model

STREAM patient-cost data were collected at two sites in Ethiopia (St. Peter's Specialized Hospital and Armauer Hansen Research Institute Hospital, both in Addis Ababa), using questionnaires adapted from the STOP-TB questionnaire [14]. Data were collected from November 2012 to December 2017. Timings of different activities such as patient travel to/from health facilities were also collected.[10] Both health system and patient costs associated with the three treatment strategies were calculated by applying the relevant unit costs (table 3) to the pathways of the 1000 patients, generated by the DES model.

Health system costs

Regimen costs, tests costs, health worker costs, consumables costs, outpatient social support costs (as they are paid by the health system), travel costs for patient-centred and hybrid strategies and costs related to hospitalisation were included in the health system costing. The unit costs for each of the categories above were taken from STREAM and updated to 2021 prices (using consumer price index) [15] (table 3). The units for each category, including staff time per visit were derived from STREAM, with the exception of the clinical and safety tests. As STREAM was a clinical trial, these tests were conducted more frequently than in routine care, so in accordance with the 2022 operational handbook on tuberculosis [16], we assumed that the clinical and safety monitoring was taking place once a month.

In STREAM, all patients were travelling to the health facility for both DOT and clinical care and the timing of these visits were collected. Hence, to calculate total travel costs for health workers in the patient-centred and hybrid strategies we assumed that the journey times and costs were equal to those of patients in STREAM. As health worker travel time was considered to count towards their working time, we also added the health worker travel-related costs calculated as minutes spent travelling times their wage per minute.

MDR-TB outpatients in Ethiopia receive a monthly social support payment to encourage treatment adherence and to compensate for lost income. A social support cost of USD38.37 to the health system, calculated as the monthly payments times the number of months under outpatient treatment was therefore applied.

The mean health system costs per patient treated are presented.

Patient costs

Patient direct costs related to transport and supplementary food were included. Transport costs were calculated for each strategy by multiplying the mean cost of a single health facility visit by the number of visits made. The weekly costs associated with the supplementary food expenditure, as collected in STREAM, was multiplied by the number of weeks of outpatient treatment for each strategy.

MDR-TB patients in Ethiopia do not incur direct medical costs (medication, hospitalisation costs) and these were computed under health system costing.

We have not included patient direct medical costs (medication, hospitalisation costs) as in Ethiopia these are not paid by the patients who are under MDR-TB treatment. We have included these in the health system costing.

Patient indirect costs (i.e. income loss for not being able to attend work) were calculated by multiplying the mean income per minute as revealed by the patients in the STREAM trial with the number of minutes spent seeking care (this included transport to and from DOT facility or health centre and time spent inpatient for the strategies where this was applicable).

The mean patient costs per treatment duration are presented.

Sensitivity and scenario analyses

Costs used in this analysis are context-specific, so we varied in a multi-way deterministic sensitivity analysis the costs related to patient indirect costs, staff costs, transport costs and inpatient stay costs.

Also, as outpatient treatment is becoming increasingly common, we eliminated the initial inpatient stay duration from standard-of-care to understand how results would change.

A second scenario analysis was included on the frequency of DOT delivery (from daily to weekly) to explore the additional cost savings for the health system.

RESULTS

Patient pathways

The average times spent in each of the treatment states for the three patient management strategies generated by the DES model can be seen in table 4. The corresponding health system and patient costs per four-week interval are also in table 4.

Health system and patient costs

Table 5 shows the overall per patient average health system and patient costs for the 9-month MDR-TB treatment of the three main treatment strategies and two further variants.

The patient-centred and hybrid strategies are less costly than the standard-of-care, from both a health system perspective (i.e. USD3037 for standard-of-care vs. USD2818 for patient-centred and USD2761 for hybrid strategies) and a patient perspective (i.e. USD589 for standard-of-care vs. USD77 for patient-centred and USD368 for hybrid if patients have a guardian).

The patient costs are lower in the hybrid and patient-centred strategies because patients are travelling less or not at all for treatment-related purposes. Guardian accompaniment caused some increase in patient costs, from 4% for the patient-centred strategy to 27% for the standard-of-care. Total costs of a patient with a guardian in the standard-of-care represent 47% of an estimated annual income of USD1248.

Sensitivity and scenario analyses

Sensitivity analyses showed that varying certain costs in a deterministic sensitivity analysis did not change the conclusions, with standard-of-care still being the most expensive strategy from both a health system and patient perspective (table 6).

Moreover, the results did not change when we assumed no hospitalisation at treatment initiation for standard-of-care. Although standard-of-care became cheaper from a health system perspective than both patient-centred and hybrid, it was still more expensive for the patients and more expensive overall (table 7).

Scenario analysis showed that reducing the frequency of DOT in the patient-centred strategies could further reduce health system costs by USD121 for patient-centred and USD68 for the hybrid strategy (table 4).

DISCUSSION

We have built an operational model of different MDR-TB treatment delivery strategies, calculating the times patients spend in eight different states during their treatment in Ethiopia. Using STREAM cost data, we have then calculated the costs of the three alternative strategies for delivering TB treatment: a strategy reflecting the current standard-of-care in Ethiopia, a patient-centred approach and a hybrid approach. We showed that patient-costs can be reduced under a hybrid or patient-centred approach. Apart from reducing the costs, these strategies have the potential to increase access to MDR-TB services, contributing to TB elimination. This study adds on the growing evidence that a decentralised model of care in Ethiopia contributes to an increase in number of people tested and put on MDR-TB treatment.[17]

However, treatment delivered at home/work might not be appropriate for patients with severe TB disease, extremely infectious or for those who have serious comorbidities. Similarly, people who have access to electricity, internet and are technologically literate can benefit from the use of video-recorded DOT or other electronic means of observing treatment. It is therefore helpful for the treating clinician to have a few options to choose from when deciding on how treatment is best delivered for each patient. A hybrid approach, as modelled in this study, with the intensive phase of treatment monitored daily as in the standard-of-care (although not in hospital), could be appropriate for most patients. Several studies suggest that fully decentralised care for TB patients, where patients are being treated as outpatients and receive care in the community is less costly than the centralised approaches, where inpatient care is provided at specialised facilities.[18][19][20] In this study, we showed that semi-decentralised (hybrid strategy) or fully decentralised (patient-centred strategy) care, with treatment for RR-TB, delivered at patients' home, can also be less costly (than the standard-of-care) from a societal perspective when DOT is delivered either daily or once a week.

Currently, patients incur substantial costs when accessing treatment which are often catastrophic despite the End-TB target of having no families affected by TB-related catastrophic costs. Appropriate social protection mechanisms could be provided to assist patients in coping with these costs and end TB. [21] We showed in this paper that switching to a new treatment delivery strategy,

with the same level of contact as in the standard-of-care, but with DOT delivered at patients' home, could shift costs from patients to the health system. Furthermore, a reduction in the number of DOT visits, from daily to weekly combined with the hybrid or patient-centred approach would further reduce health system costs.

While TB diagnosis has been previously modelled using operational models [22], the present study has demonstrated that TB treatment delivery strategies can also be successfully modelled using this approach. Having been built with a user-friendly Excel interface, the model can be easily adapted in future as new data become available, and new strategies require evaluating. For example, any of the unit costs in table 2 can be revised and recombined with the average phase durations (also in table 2) to give revised costs of treatment equivalent to those in table 5. For TB, this will be critical in the coming years as treatment duration is being reduced and treatment delivery redesigned. The model can also be used to show the distribution of patients' experiences as they move through the alternative treatment strategies, including for example the range of lengths of their patient journeys and their associated costs.

It is important that we highlight several limitations of our modelling. Our results find the patient-centred and hybrid strategies cost-saving, although our modelling has likely overestimated their costs. First, we assumed the nurses providing DOT in the hybrid and patient-centred strategies at patients' homes were equally as qualified as nurses in healthcare facilities today. However, treatment could likely also be delivered by community health workers, volunteers, or treatment supporters, which would cost the health system less. Furthermore, there are also potential health benefits our study has not captured: studies have estimated a reduced rate of loss-to-follow-up under a decentralised treatment delivery system with less frequent DOT visits, compared to a centralised approach,[18][19][20] which we did not account for in our model.

Second, we assumed treatment success rate to be independent of treatment management strategy. However, a 2017 systematic review showed that treatment success was more likely in patients following a decentralised setting.[23] The Loveday et al [20] study also showed that a decentralised model results in better clinical outcomes. The same study also showed that there was a reduced lost-to-follow up for those following a decentralised pathway, while other studies reported similar estimates versus centralised approaches [24][25].

Ancillary costs such as those related to minimising transmission were not included. If strategies such as those we modelled were to be implemented, a policymaker may choose to include some infection control education at household level. However, such a scheme's cost would be unlikely to exceed USD264 per patient treated —the difference between the standard-of-care and patient-centred strategy — and so would be unlikely to alter the conclusions of our study.

Increasingly more patients are being diagnosed with MDR-TB globally each year. While undergoing an often-challenging MDR-TB treatment regimen, these patients and their families currently must withstand an additional severe burden on household finances. [26][27] TB programmes urgently require strategies able to reduce these costs. Our findings provide critical evidence that there is scope for such strategies based on the reorganisation of patient care. Patient-centred treatment delivery for MDR-TB could be the first step of an integrated patient-centred care system, where patients are getting tested and diagnosed with MDR-TB in the community, thanks to the expansion of Xpert/MTB/RIF use, that simultaneously detects *M. tuberculosis* and resistance to rifampicin. This would be a practical approach for scaling up treatment and care for the MDR-TB patients.

CONCLUSION

Now, more than ever, TB programmes need a rethink on how MDR-TB treatment is delivered. Our findings show that patient and health system costs can be reduced by implementing patient-centred approaches to deliver MDR-TB treatment. These results should be used to inform country-level decisions on delivering MDR-TB care and potential phase-IV evaluations.

Abbreviations

DOT- directly-observed treatment

DES- discrete event simulation

MDR-TB- multidrug-resistant tuberculosis

SAE- serious adverse event

STREAM- Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB

TB- tuberculosis

US- United States

Declarations

Ethical approval

All data used are publicly available; no ethical review was sought.

Funding

No funding was received for conducting this study.

Contributors

LR made substantial contributions to the conception of the work, acquisition of the data, analysis and interpretation of data and contributed to the drafting of the work and revised it critically for important intellectual content. LM, ET, CW, DW, MJ made substantial contributions to the simulation model development, analysis and interpretation of model outputs and also contributed to the drafting of the work and revised it critically for important intellectual content. JN contributed to the analysis and interpretation of data for the work and revised the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

All authors gave final approval for this study to be published.

Competing interests

Authors have no competing interests to declare.

Availability of data and materials

The data used during the current study are publicly available and can be found in the STREAM economic evaluation paper (http://dx.doi.org/10.2471/BLT.19.243584). Model probabilities have been calculated using data from the STREAM clinical paper (https://www.nejm.org/doi/full/10.1056/nejmoa1811867).

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Not applicable

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Table 1^. Location of care received, by treatment phase, for each of the treatment delivery strategies included in the model

Strategy	Standard of care		Hybrid		Patient-centred	
Treatment Phase	IP	CP	IP	CP	IP	CP
Treatment initiation#	In hospital	N/A	At the health facility	N/A	At the health facility	N/A
DOT location~	At the health facility	At the health facility	At the health facility	At patient's home or workplace	At patient's home or workplace	At patient's home or workplace
Treatment monitoring location¬	At the health facility	At the health facility	At the health facility	At patient's home or workplace	At patient's home or workplace	At patient's home or workplace

IP= Intensive Phase, CP= Continuation Phase, N/A= not applicable

#Treatment initiation is represented by the first four weeks of treatment

¬Treatment monitoring takes place once a month for all strategies

~DOT visits take place daily for all strategies

^Table 1 was not included in the version submitted to the journal

Table 2. Monthly Probabilities of serious adverse events, conversion rates and deaths used in simulation model, by week period

Period (weeks)	Prob (SAE)¬	Prob (Convert)^	Prob (Death and dropout)[
1 to 4	0.0175	0.62	0.013
5 to 8	0.0175	0.62	
9 to 12	0.0175	0.27	
13 to 16	0.0175	0.27	
17 to 20	0.0101	0.27	
21 to 24	0.0101	0.27	
Up to week 48	0.0101	N/A ~	

~N/A is not applicable as patients who have not converted by week 24 were excluded from the model

¬As SAEs are more likely during the intensive phase (weeks 1 to 16) than in the continuation phase, we considered the two period separately when calculating the probabilities. This was done under the assumption that no SAE can happen in consecutive months, but can happen a month apart.

^As high number of patients were converting in the first 8 weeks, we assumed a constant, higher probability in the first eight weeks and lower afterwards.

[l] *Probability of death and dropout are for each four-week interval. We assumed a constant probability throught the treatment duration. Death and dropout have been collated as in both cases the patients exit the model.*

Table 3. Unit costs used in calculating health system and patient costs

Cost category	Unit	Unit costs (USD, 2021)
Health system costs		
Regimen cost	Per full treatment course	1494.99
Hospitalisation hotel cost	Per day	2.55
Hospitalisation meal	Per day	7.35
Sputum smear	Per test	1.48
Sputum culture	Per test	34.48
LFT	Per test	2.64
Serum Creatinine	Per test	1.91
TSH	Per test	6.84
X-ray	Per test	13.3
ECG	Per test	10.95
Serious adverse event	Per episode	22.07
Nurse cost per minute	Per minute	0.01
Doctor cost per minute	Per minute	0.02
Consumables cost per visit	Per visit	2.64
Overheads	Per month	152.96
Outpatient social support cost	Per month	38.37
Patient costs		
Mean transport cost	Per return visit	0.88
Supplementary food expenditure	Per week	1.17
Income	Per minute	0.01

LFT = liver function test, TSH = thyroid stimulating hormone, ECG = electrocardiogram

Table 4. Mean costs (in USD) per month by phase of treatment and average phase durations (in months)

	Treatment state							
	1 IP in hospital	2 IP at home	3 IP SAE in hospital	4 IP SAE home	5 Extended IP	6 Extended IP and SAE	7 CP at home	8 CP SAE in hospital
Standard-of-care								
Health system	755.2	368.8	770.6	770.6	368.8	770.6	169.8	571.6
Patient	134.4	31.0	134.4	134.4	31.0	134.4	31.0	134.4

Patient with guardian	134.4	57.3	134.4	134.4	57.3	134.4	43.1	134.4
Time spent in state	*1.607*	*2.254*	*0.026*	*0.018*	*0.128*	*0.003*	*5.216*	*0.041*
Patient-centred with weekly / daily DOT visits								
Health System	0	397.8/ 411.0	0	798.5	397.8/ 411.0	798.5	198.8/ 212.0	599.5
Patient	0	6.6	0	134.4	6.6	134.4	6.6	134.4
Patient with guardian	0	7.3	0	134.4	7.3	134.4	6.6	134.4
Hybrid with weekly / daily DOT visits								
Health System	0	396.7	0	798.5	396.7	798.5	198.8/ 212.0	599.5
Patient	0	31.0	0	134.4	59.0	134.4	32.6	134.4
Patient with guardian	0	45.3	0	134.4	73.3	134.4	32.6	134.4
Time spent in state	*0*	*3.858*	*0*	*0.055*	*0.145*	*0.003*	*5.198*	*0.042*

IP = Intensive Phase, CP = Continuation Phase, SAE = Serious Adverse Events

Table 5: Mean per-patient health system and patient costs for the three strategies (USD)

	Standard-of-care	**Patient-centred (daily DOT)**	**Hybrid (daily DOT)**	**Patient-centred (weekly DOT)**	**Hybrid (weekly DOT)**
Health System	3037	2818	2761	2697	2693
Patient	463	74	311	74	311
Patient with guardian	589	77	368	77	368
Societal, including guardian	**3626**	**2895**	**3129**	**2774**	**3061**

DOT= directly-observed treatment

Table 6: Mean per-patient health system and patient costs for the three strategies, when key unit costs have been varied in a sensitivity analysis (USD)

30% increase in staff and patient costs			
	Standard-of-care	**Patient-centred**	**Hybrid**
Health system	3059.7	2866.9	2775.8
Patient	591.7	82.9	346.8

Patient with guardian	755.0	86.9	421.2
30% decrease in staff and patient costs			
Health system	3015.1	2769.5	2720.9
Patient	334.9	64.5	275.5
Patient with guardian	422.9	66.6	315.5

446

447 Table 7. Standard of care costs when hospitalisation during the treatment initiation was eliminated
448 (USD)

	Standard-of-care
Health system	2567.6
Patient	463.3
Patient with guardian	588.9
Societal, including guardian	3156.5

449

Original Research

Cost of digital technologies and family-observed DOT for a shorter MDR-TB regimen: a modelling study in Ethiopia, India and Uganda

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ABSTRACT

WORDCOUNT (303 words)

Background:

In 2017, the WHO recommended the use of digital technologies, such as medication monitors and video observed treatment (VOT), for directly observed treatment (DOT) of drug-susceptible TB. The WHO's 2020 guidelines extended these recommendations to multidrug-resistant tuberculosis (MDR-TB), based on low evidence. The impact of COVID on health systems and patients underscored the need to use digital technologies in the management of MDR-TB.

Methods:

A decision-tree model was developed to explore the costs of several potential DOT alternatives: VOT, 99DOTS (Directly-observed Treatment, Short-course) and family-observed DOT. Assuming a 9-month, all-oral regimen (as evaluated within the STREAM trial), we constructed base-case cost models for the standard-of-care DOTs in Ethiopia, India, and Uganda, as well as for the three alternative DOT approaches. The models were populated with STREAM Stage 2 clinical trial outcome and cost data, supplemented with market prices data for the digital DOT strategies. Sensitivity analyses were conducted on key parameters.

Results:

Modelling suggested that the standard-of-care DOT approach is the most expensive DOT strategy from a societal perspective in all three countries evaluated (Ethiopia, India, Uganda), with considerable direct- and indirect-costs incurred by patients. The second most expensive DOT approach is VOT, with high health-system costs, largely caused by up-front technology expenditure.

Each of VOT, 99DOTS and family-observed DOT would reduce by more than 90% patients' direct and indirect costs compared to standard of care DOT.

Results were robust to the sensitivity analyses.

Conclusions:

While data on the costs and efficacy of alternative DOT approaches in the context of shorter MDR-TB treatment is limited, our modelling suggests alternative DOT approaches can significantly reduce patient costs in all three countries. Health system costs are only higher for VOT when compared to standard of care DOT, as low smartphone penetration and internet availability requires the health system to fund the cost of making them available to patients.

Key Words: Tuberculosis, digital technology, DOT, MDR-TB, shorter regimen, cost

Background

Tuberculosis (TB) is a disease caused by bacteria that are spread through air. Multi-drug resistant tuberculosis (MDR-TB) is caused by strains of TB bacteria that do not respond to the two most potent anti-TB drugs.[1] In 2019, at the global level, half a million people developed rifampicin-resistant TB (RR-TB), and 78% of these had MDR-TB[1]. The WHO End TB strategy[2] aims to end the global TB epidemic by 2035 and, amongst other targets, it aimed to reduce to zero, by 2020, the percentage of affected families spending more than 20% of their annual pre-TB household income seeking TB care (catastrophic costs). However, most countries did not reach this milestone. Additionally, the COVID-19 pandemic reversed progress made towards global TB targets, demanding a renewed focus on improving access to acceptable treatments and treatment success rates.

Globally, 2019 treatment success rates for drug-susceptible TB were 86% but only 60% for MDR-TB, with more than 15% of unfavourable results attributable to patients who were lost to follow-up[1]. For many years, the recommended treatment for MDR-TB included injectable agents and lasted as long as 20 months. In 2020, the WHO recommended a new shorter, all-oral (9-11 months) regimen for patients with MDR-TB and more recently a 6-month all-oral regimen[3,4]. However, the 9-month all-oral regimen is still in widespread use. Research has shown that patients find it easier to complete shorter all oral regimens, compared with previously recommended injectable-containing longer regimens[3].

Directly Observed Treatment, Short-course (DOTS) strategy has been recommended by the WHO since 1993. It has been a successful approach to TB control in many countries. Traditionally, in-person observation of patient treatment adherence by health professionals (SOC DOT) was a key component of the DOTs strategy[5]. In 2017, to address patient and health system needs, however, the WHO Global TB Programme formulated new recommendations for DOT of drug-susceptible TB (DS-TB)[6] to make it more patient-centred. Key aspects of the updated guidelines recommend the use of electronic and mobile phone applications, known as digital health interventions. These have been used successfully to improve treatment adherence in the context of HIV and NCDs[7,8], and can include use of Short Message Services (SMS) or phone calls for medication reminders, medication monitors, and video-observed treatment (VOT). The 2020 MDR-TB guidelines extended the digital intervention recommendations to MDR-TB, acknowledging their potential contribution to making MDR-TB management more patient-centred[9]; however, the 2020 recommendations rated the certainty of evidence supporting the use of digital interventions to support adherence as very low. A WHO review of community contributions to TB care and recommendations to national TB programmes mentions that family members can act as DOT supervisors.[10]

There is some evidence that VOT and MM can achieve similar treatment completion rates as SOC DOT in patients being treated for DS-TB, with similar numbers of missed doses. There is also limited evidence that family-observed DOT can achieve similar treatment success in MDR-TB patients who

received the longer 20-24 month regimen. However, the cost, cost-effectiveness and effect on adherence and clinical outcomes of these interventions in the context of shorter MDR-TB regimens are unknown (see supplement).

There is however some evidence that digital health interventions can improve treatment adherence in people with drug-susceptible TB; however, no effect on clinical outcomes (cure, failure, death) has been observed[11].

This paper evaluates the cost of the three of the most used alternatives to SOC DOT- VOT, 99DOTS (a real time remote monitoring of intake of TB treatment using low-cost mobile phone-based technology) and family-observed DOT- for patients receiving a 9-month, all-oral MDR-TB treatment as tested in STREAM Stage 2 and that is similar to the WHO recommended regimen in 2020. It is thought these interventions enhance the patient's autonomy, while still enabling health workers to monitor treatment adherence. Moreover, due to the longer duration of MDR-TB treatment and considerably higher costs of treatment borne by MDR-TB patients compared to DS-TB patients[12], the potential benefits to MDR-TB patients of alternative DOT approaches are likely to be even greater than for drug-susceptible TB.

Methods

Study setting

Ethiopia, India and Uganda are three of the 30 high TB burden countries, with an MDR/RR-TB incidence, in 2021, of 1800 cases (95% CI 1100-2500), 119 000 (95% CI 93000- 145 000) and 1500 (95% CI 450- 2500), respectively[1,13]. All three countries use a bedaquiline-based 9-month all-oral regimen similar to the STREAM 2 regimen as their standard of care for MDR-TB, and hadSTREAM Stage 2 study sites. STREAM was the largest recruited clinical trial to examine shortened regimens for MDR-TB.

In all three countries, most MDR-TB patients initiate treatment for MDR-TB at a TB hospital as outpatients and their treatment is then monitored by the district TB programs. Outpatient treatment is typically delivered using SOC DOT, meaning that MDR-TB patients travel daily in Ethiopia and Uganda and three times a week in India, to district health centres where they receive and take their TB medication. Usually, these district health centres are not fully decentralised to the patient's community, so patients will incur out-of-pocket expenses for transport and/or food[14,15] and income loss to take their treatment. This can have a substantial cost for patients, impact other competing activities in a patient's life (opportunity cost) and also lead to missed doses or loss to follow-up (LTFU)[16].

Description of Interventions

In this study we evaluate VOT, 99DOTs and family-observed DOT compared to SOC DOT. These interventions were selected based on a 2018 systematic review[17] which showed that VOT and medication monitoring (MM) achieved similar treatment completion rates as SOC DOT in patients being treated for DS-TB, with similar numbers of missed doses.

When access to technology is limited, family-observed DOT can be an alternative to digital DOT. [10] A study showed no statistically significant difference in terms of treatment success as compared to SOC DOT (Family-observed DOT: 72%, 95% CI: 31.5- 93.5%; SOC DOT: 65.8%, 95% CI 55.7- 74.7%) in

MDR-TB patients receiving the longer (20-24 month) treatment[18]. Little or no difference was observed in cure or treatment completion rates.

VOT

VOT is a smartphone-based approach that allows for remote treatment monitoring through either live or patient-recorded videos.

Studies conducted in the US and UK[19,20] for DS-TB reported higher adherence with VOT, including in vulnerable populations. However, in the US, the effect on treatment completion rates was not statistically significant [21]. VOT substantially reduced healthcare personnel time needed for DOT supervision in both studies.

99DOTS

99DOTS employs a low-cost mobile phone-based technology that enables real-time remote medication monitoring.[22] The anti-TB drugs blister packs are wrapped in a custom envelope that, when dispensing pills reveals hidden phone numbers. Patients then use any phone to call the number revealed, at no cost. The call is automatically recorded in the patient's file and used to track adherence.

A large randomised controlled trial[11] of treatment support for active, DS-TB conducted in China reported that MM had an effect on treatment adherence relative to SOC DOT, with 29.9% of doses missed in the SOC DOT arm versus 17.0% in the medication monitor arm. However, there was no demonstrated impact on clinical outcomes. Since 2018, this DOT approach has been widely used in India for DS-TB, with more than 200,000 patients enrolled[22]. Amongst its benefits are the greater convenience and reduced stigma for patients[23].

Family-observed DOT

Under family-observed DOT daily treatment is supervised by a household member or friend selected by the patient, with drugs provided to the family member supervisor every two weeks. This reduces the patient's visits to the DOT facility and stigma associated with visiting the centre on a daily basis[24]. Randomised controlled trials showed that there was no significant difference between treatment success rates of SOC DOT versus family-observed DOT in DS-TB patients.[25]

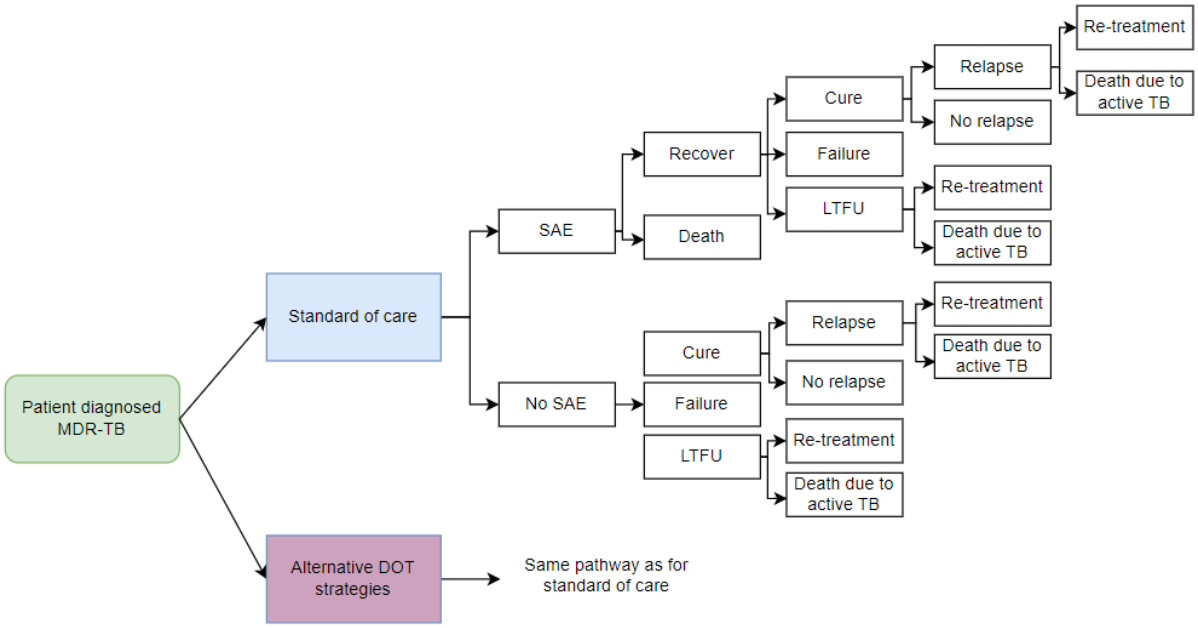
Description of SOC DOT

MDR-TB patients initiate treatment at a TB hospital and, after the intensive phase, their treatment is then monitored by the district TB programs. Health workers at the district TB programs then deliver and supervise treatment. To receive treatment, patients travel daily in Ethiopia and Uganda and three times a week in India, to the DOT facility, incurring both direct and indirect costs.

Decision analytic model

A decision analytic model was developed in Excel (Figure 1) to compare the costs of the above-mentioned DOT approaches in Ethiopia, India and Uganda. Costs were evaluated for patients receiving the 40-week, all-oral MDR-TB regimen, as evaluated in the STREAM Stage 2 trial, to construct the base-case standard of care DOT model in each country.[26]

Figure 1. Visual representation of decision analytic model of standard of care and alternative DOT approaches



Source: Authors. Acronyms: SAE- Serious Adverse Event, LTFU- lost to follow-up. Final outcomes follow WHO categories: cured, failure, LTFU or death. Failure is defined as unfavourable outcomes as a result of treatment extension longer than 8 weeks after adverse event, or extension or change for other reasons, including adverse event, or consent withdrawal, lack of culture conversion and bacteriological reversion on treatment. Cure is defined as a treatment outcome that is not failure or LTFU. Relapse is defined as bacteriological reversion on treatment. Death was considered an SAE.

Several key assumptions were incorporated into the model. It was assumed that all DOT approaches yield the same cure, failure, LTFU and death rates. We made this assumption because there is no reported evidence regarding the impact of alternative DOT approaches on treatment outcomes for shorter MDR-TB regimens. It was also assumed that all patients are treated as outpatients during the whole treatment period, as this reflects usual practice in all three countries. There is some evidence that SAEs result in treatment extension[27], so we have therefore assumed that treatment can be extended by 8 weeks, the maximum period allowed in the trial before an outcome was categorised as unfavourable.

Total number of DOT visits for each strategy was 280 in Ethiopia and Uganda, and 120 in India. For SOC DOT, those visits were in person; for the alternative DOT strategies, those “visits” were virtual or in person in the patient’s home (for family-observed DOT). In addition to DOT visits, in accordance with the 2022 operational handbook on tuberculosis, the model assumes patients travelled monthly to health facilities for in person clinical and safety monitoring, adding an additional nine in person visits/patient to the DOT visits for each approach (see supplement for details on the tests done).[28]

Probability of different treatment outcomes and SAEs for the 9-month regimen were calculated based on the STREAM Stage 2 trial outcomes (Table 1).[29]

Table 1. Probabilities used in the model, derived from the STREAM Stage 2 trial outcomes

Parameters	Probability
Probability of SAE	0.18
Probability of cure if no SAE	0.86
Probability of failure if no SAE	0.11

Probability LTFU if no SAE	0.03
Probability of recovering after SAE	0.82
Probability of death after SAE	0.18
Probability of relapse after cure after SAE	0.02
Probability of no relapse after cure after SAE	0.98
Probability of relapse after cure	0.02
Probability of no relapse after cure	0.98
Probability of cure after SAE	0.85
Probability of failure after SAE	0.12
Probability of LTFU after SAE	0.03

In addition to this, a 10% probability of death due to untreated active RR-TB after relapse was applied.[1]

Cost data

Main cost data source was STREAM Stage 2 trial data, supplemented by market prices or published estimates for costing alternative DOT strategies (see supplement).

Health system costs

For costing VOT, we used market prices in each country in costing the smartphones and mobile data required. We assumed a 5-minute appointment duration for each VOT visit[30]; for a video call of this duration, it was calculated that 500MB of data per patient per month would be needed.[31] Monthly data usage was costed using in country data bundle costs. Smartphone penetration rates (more than 70% of Ugandans,66% of Ethiopians and 57% of Indians did not own a smartphone in 2021) and internet usage data were used to calculate the percentage of population requiring a device and mobile data. To this, we added the costs related to the staff performing the monitoring activities for each strategy.

For costing 99DOTS, we included the per patient fixed cost of renting a toll-free line, the envelopes costs, SMS, call and staff packaging costs from manufacturer published data[22]. As for 99DOTS there is no need for a manned call, only costs related to healthcare worker training and adherence monitoring were included, assuming a 15-minute duration per dose per patient.

For family-observed DOT costs, it was assumed that the family-member did not receive any pay for supervising their relative's treatment. It was also assumed the family member was trained at the beginning of treatment and then every 12 weeks on how to monitor treatment adherence. Staff time of healthcare workers conducting that training was also included.

For SOC DOT, staff costs were calculated assuming a 15-minute in-person visit duration.

Mean SAE costs from STREAM were added to the health system costs in each country. Also, costs related to monitoring tests and quantities and resources used during the in-person visits were also from STREAM (see supplement).

Patient costs

Both direct and indirect patient costs were included.

In terms of direct costs, we included the costs for attending DOT visits and monitoring visits, as reported by patients in the STREAM trial, up until week 40 of treatment. No costs related to post-treatment follow-up were included.

For calculating indirect costs, we used patient-reported income before MDR-TB diagnosis from STREAM.

Societal costs were calculated by summing total health system and patient costs.

Sensitivity analyses

We conducted probabilistic sensitivity analysis to assess parameters uncertainty (see supplement) using 1000 Monte Carlo simulations. We fitted beta distributions for probabilities and gamma for costs. Where ranges were not available for costs, we used +/-30% as a range for mean costs. (S

The digital DOT and family observed DOT approaches are generally better accepted by patients, improving their commitment to treatment. This in turn can reduce the LTFU rates compared to SOC DOT. Therefore, we varied this parameter in a deterministic sensitivity analysis, by reducing the LTFU rate in the digital DOT and family observed DOT by 5% and 10%. However, DOT that is not supervised by a health worker might result in worse medication adherence, so in the sensitivity analysis we also tested a higher recurrence rate, by 6.5%, compared to the base case, for the alternative DOT strategies.[32,33,34]

Results

All base case results are in table 2.

Table 2. Health system, patient and societal costs for each DOT strategy in each country

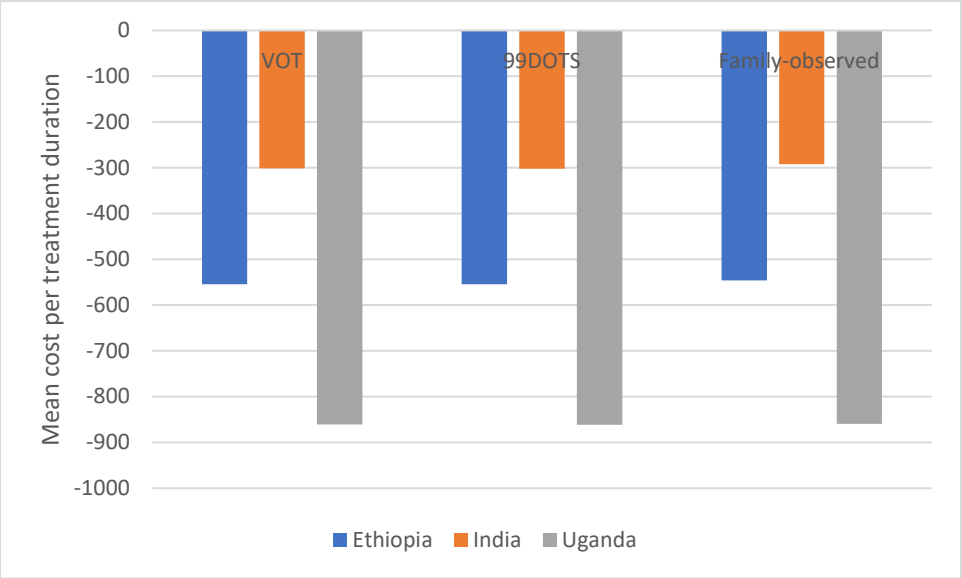
	Ethiopia (US$)			India (US$)			Uganda (US$)		
	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3790.4	572.3	4362.6	2003.3	324.2	2327.4	6348.6	888.6	7237.1
VOT	3999.9	17.9	4017.8	2201.7	22.7	2224.4	6716.7	27.7	6744.5
99DOTS	3769.3	17.9	3787.2	1980.4	22.1	2002.5	6151.2	27.4	6178.7
Family-observed	3765.4	26.3	3791.7	2005.0	31.8	2036.7	5975.0	29.5	6004.4

Patient costs

When compared to SOC DOT, adoption of VOT or 99DOTS reduces patient costs by 97% in Ethiopia and Uganda, and by 93% in India.

Although family-observed DOT is slightly more expensive than VOT and 99DOTS in all countries due to the monitoring training required, it would still save patients over 90% of costs in all countries when compared to SOC DOT (figure 2).

Figure 2. Patient costs (in US$) of the different treatment delivery strategies compared to SOC



Health system costs

From a health system perspective, VOT was the most expensive DOT strategy, with a cost increase ranging from 5% in Uganda to 10% in India when compared to SOC. Higher health-system costs for VOT were primarily driven by up-front technology expenditure to purchase smartphones for patients because of low smartphone penetration rates.

Health system costs for the 99DOTS were slightly lower than SOC in all three countries, with savings ranging from 1% in Ethiopia and India to 3% in Uganda. This is due to a slight reduction in staff costs, as 99DOTS requires reduced staff contact time.

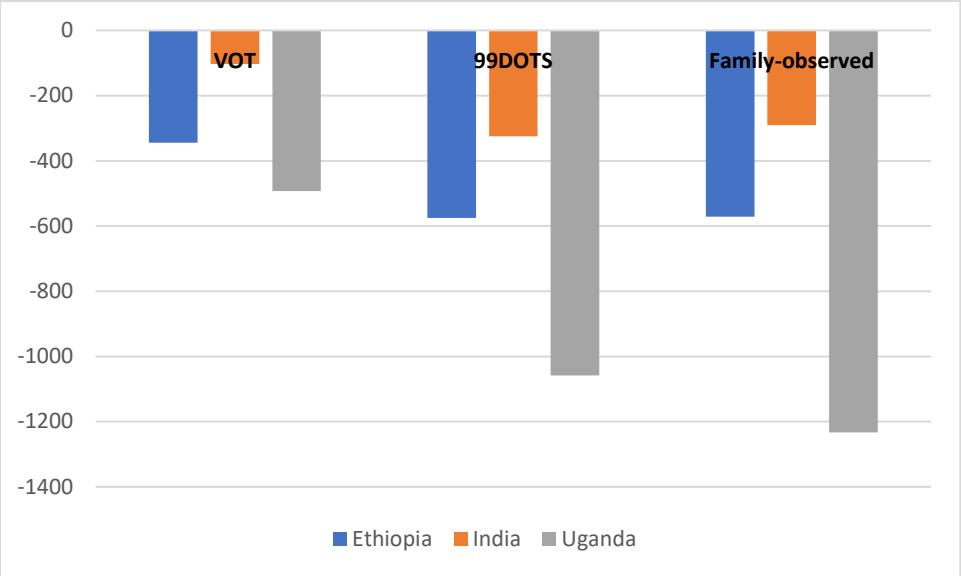
With respect to health system costs, family-observed DOT was the cheapest strategy when compared to SOC DOT in Ethiopia and Uganda (1% cheaper in Ethiopia and 6% in Uganda). In India, this strategy was slightly more expensive than SOC DOT, by 0.1%.

Societal costs

From a societal perspective, SOC is the costliest approach in all three countries (Figure 2). This is closely followed by the VOT approach, with savings vs. SOC DOT ranging from 4% in India to 10% in Ethiopia.

Family-observed DOT yields the highest savings vs. SOC DOT from a societal perspective in Uganda, while 99DOTS is the cheapest strategy in Ethiopia and India.

Figure 2. Societal costs of alternative DOT strategies compared to SOC



Sensitivity analyses

Decreasing the LTFU by 5% and 10% made the alternative DOT approaches less costly than in the base case as a consequence of slightly lower health system costs (see supplement). This is because lower patients will need re-treatment.

Results remained robust to an increased relapse rate of 6.5%, although the health system costs for the alternative DOT approaches costs increased (see supplement) as the number of patients needing re-treatment increased.

Findings also remained robust when parameter uncertainty was tested in a probabilistic sensitivity analysis.

Discussion

This study analyses the potential cost of implementing alternative, more people-centred DOT approaches for MDR-TB patients that follow a 9-month all-oral treatment regimen. The results indicate that use of VOT, 99DOTS and family-observed DOT as part of a 9-month all-oral MDR-TB treatment regimen could result in important societal cost savings and substantially reduce patient costs in all countries. This could protect TB-affected populations from catastrophic expenditure. The results are consistent with other studies[35], which reported societal cost savings of 15% to 18% from the use of alternative DOT approaches, compared to SOC DOT for the long MDR-TB treatment recommended by the WHO in 2011 (now superseded).

SOC DOT requires patients to regularly visit health facilities for DOT, placing a significant cost burden on patients[12] and potentially contributing to LTFU. A qualitative study in Ethiopia reported that traveling long distances to a health facility for SOC DOT generated patient costs that competed with other essential expenses and made it difficult for patients to collect their daily drugs. In that study, patients stated that lack of money for travel to health facilities was the main reason for treatment non-compliance.[16] Other studies reported that patients found SOC DOT inconvenient and preferred VOT over SOC DOT.[36,37] In contrast, the alternative DOT approaches evaluated in this study permit DOT to take place according to the patient's circumstances, limiting interruptions to their usual activities while also achieving the same objectives as SOC DOT (i.e., reminding patients to take their medication and/or permitting healthcare workers to monitor treatment adherence). From a health

system perspective, VOT and 99DOTS have robust, electronic, data-monitoring systems that can be implemented, possibly making it easier for healthcare workers to monitor treatment adherence and reduce time allocated to this activity.[20] This is in contrast with SOC DOT, which typically uses paper-based treatment cards to record treatment adherence, making data monitoring more time consuming and less efficient.

In the base case model, we assumed that health system costs would remain constant for each new MDR-TB patient, i.e., that mobile phones and data will be bought for all patients who do not own them at treatment initiation. However, VOT and 99DOTS costs could decrease gradually as ownership of mobile phones increases or insurance systems to ensure return of smartphones are put in place. Moreover, some costs, such as renting a toll-free line for 99DOTS or mobile data costs could decline on a per patient basis due to economies of scale as more patients are allocated to the alternative DOT approaches. This would result in additional per patient cost savings for the alternative DOT approaches, when compared to SOC. Additionally, a model similar to the one in the UK[19] could be implemented, where patients pre-record a video while taking the pills and healthcare workers only randomly check 20% of them. This could further reduce health system costs but can also affect treatment adherence.

Adopting digital healthcare approaches, thus increasing access to a smartphones and internet connections, may also have benefits beyond DOTs for the patients, such as growing access to education or increasing ease of communication.

This study has a number of limitations. As there is no study assessing the efficacy of the different DOT approaches in the context of shorter MDR-TB regimens, we assumed that DOT strategies would not affect treatment outcomes. Although we tested these assumptions in the sensitivity analyses, more research is needed to understand the efficacy and cost-effectiveness of the alternative DOT strategies, particularly in LMIC countries. Until that research is undertaken, it is difficult to assess the cost-effectiveness of the various DOT approaches presented in this paper. It is possible that these approaches might reduce LTFU and because they are also cheaper, they would be highly likely to be cost-effective compared to SOC DOT. The alternative DOT approaches might also result in more missed doses and thus in worse clinical outcomes, such as increased relapse rates. If this is the case, then the reduced efficacy of alternative DOT strategies might offset their lower cost.

VOT and 99DOTS can only be implemented when the required technology is available and can be appropriately organized and operated by health care providers and patients. This would require patients to have an electricity source to charge their devices (at a minimum). In some countries/populations, this may not be possible for all patients. In those cases, a potential alternative to this is family-observed DOT, which provided substantial societal cost savings in our modelling exercise when compared to SOC DOT.

There are costs that were not captured in the model, including increased utility bills for patients due to higher electricity usage for charging equipment. It also does not include costs related to the training required for patients to use digital technologies, the training required for healthcare workers regarding alternative DOT strategies, or the cost to develop digital treatment monitoring protocols. These are difficult to estimate and would likely differ by country.

Ethics approval and consent to participate

Ethics approval was not sought for the present study because it used only published data.

Consent for publication

Not applicable

Availability of data and materials

The data used during the current study are publicly available and can be found in the STREAM economic evaluation paper (https://doi.org/10.1016/S2214-109X(22)00498-3), 99DOTS paper (https://www.microsoft.com/en-us/research/uploads/prod/2019/02/99DOTS-ICTD.pdf), Ethio Telecom (https://www.ethiotelecom.et/), MobGSM (https://et.mobgsm.com/mobile/samsung-galaxy-a13-price-in-ethiopia), Airtel (https://www.airtel.in/), Croma (https://www.croma.com/phones-wearables/mobile-phones/c/10) and Jumia (https://www.jumia.ug/). Model probabilities have been calculated using data from the STREAM clinical paper (https://doi.org/10.1016/S0140-6736(22)02078-5). More details are in table 1 of the main paper and tables S1 and S2 of the supplement.

Competing interests

No competing interest to declare.

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Authors' contributions: LR made a substantial contribution to the conception and design and conduct of the study. She carried our data analysis and interpretation. She designed the figures and tables, produced the first draft of the manuscript and incorporated critical feedback and revision form coauthors. JJM, GB, BS and EW made a substantial contribution to the study analysis and interpretation and critiqued the manuscript for important intellectual context. JN, MG and MM critiqued the manuscript for important intellectual context.

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Supplementary Appendix

1 CONTENTS

2 LIST OF ABBREVIATIONS

ALT- Alanine Transaminase

AST- Aspartate Transferase

DOT- Directly-observed treatment

ECG- Electrocardiogram

MDR-TB- Multidrug resistant tuberculosis

SAE- Serious Adverse Event

SOC- Standard of care

STREAM- The Standardised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB

TB- Tuberculosis

VOT- Video-observed treatment

WHO- World Health Organization

3 LISTING OF SUPPLEMENTARY TABLES AND FIGURES

Table S1: Unit costs used in calculating health system costs

Table S2: Unit costs used in the analysis that were tested in the probabilistic sensitivity analysis
Table S3: Scenario analysis where smartphone costs were eliminated from the health system costs

Table S4: Scenario analysis for a 6-month all-oral regimen

Table S5: Probabilistic sensitivity analysis results

Table S6: Deterministic sensitivity analysis on LTFU and relapse rates for the digitally-observed DOT and family-observed DOT

Figure S1: Health system costs compared to standard of care for each of VOT, 99DOTS and family-observed DOT, in each country

4 BACKGROUND

WHO recommended the use of digital technologies, such as medication monitors and video observed treatment for directly observed treatment of drug-susceptible TB since 2017. These recommendations were extended with the 2020 guidelines[1], but without good evidence on either the cost or effects of these for the shorter MDR-TB regimen.

We searched PubMed for studies on digital DOT or family-observed DOT in the context of MDR-TB published from June 2020 when the all-oral, shorter MDR-TB regimen was recommended by WHO to December 2022, with the terms "tuberculosis" AND "rifampicin resistance" OR "rifampicin-resistance" OR "rifampin resistance" OR "rifampin-resistance" OR "MDR" OR "multidrug" OR "multi-drug" OR "MDR-TB" OR "RR-TB" AND "digital health" OR "video observed" OR "video-observed" OR "99DOTS" OR "VOT" OR "video monitoring" OR "message reminders" OR "family DOT" OR "medication monitor" AND "treatment adherence" OR "cure" OR "completion" OR "compliance" OR "cost". This searched yielded 46 results but none of the studies evaluated treatment outcomes or costs of digital DOT or family-observed DOT for the 9-month all-oral regimen; some studies included longer MDR-TB treatment regimens or focused chronic respiratory disease.

Prior to this study, there was evidence that a longer MDR-TB treatment delivered via digital interventions led to cost savings relative to standard of care DOT in Brazil.[1] Few other studies compared SOC to digital DOT for drug-susceptible TB. [2,3,4,5,]

Supplementary details of the methods and results presented elsewhere, are reported below.

5 DETAILED METHODS

All costs are reported in 2021 US$.

The local guidelines recommend daily DOT visits in Ethiopia and Uganda and three DOT visits weekly once injectable-containing treatment ended in India.

WHO also recommends that patients attend monthly clinical and safety monitoring visits[6]. As treatment duration was 9-months long, patients had 9 assessment visits where the following tests were done: smear test, culture, ALT, AST, CBC, Serum Creatinine, Serum Potassium, Chest X-ray, and ECG.

Our model also allows for patients who relapse for one re-treatment with the same 9-month treatment and same periodic clinical monitoring visits. Also, our model assumes that patients who are lost to follow-up and not die within one year are re-treated.

70% of people in Uganda[7], 66% in Ethiopia[8] and 57% in India[9] did not own a smartphone in 2021. These penetration rates have been used in calculating the equipment costs for delivering the VOT strategy (see scenario analyses below). Internet connection is also required for making video calls, so we calculated that a 5-minute duration for each VOT visit would require 500MB of data per patient per month and this would be bought for all patients, regardless of whether they own a smartphone or not.[10] Smartphones and mobile data costs were obtained from phone companies in each country. All unit costs used in the analysis and their sources are in tables S1 and S2.

6 SENSITIVITY ANALYSES

All probabilities were included in the probabilistic sensitivity analysis and a beta distribution was used.

When no information about the parameters was available, as in the case of costs, a distribution was constructed assuming that the 95% credible interval around the mean is represented by the mean +/-30%. Using these credible intervals, a standard error has been calculated and, using the method of moments the parameters for the gamma distribution have been derived (see table S2).

As smartphone ownership is expected to increase in the future, a scenario analysis was also conducted by eliminating the smartphone costs (but not mobile data-related costs) from the health system costs (table S3).

A 6-month all-oral regimen has recently been recommended by WHO for treating MDR-TB. Therefore, a further scenario analysis was conducted to assess how costs would change when treatment duration is reduced. Thus, total number of patient centred visits in Ethiopia and Uganda were assumed to be 180 visits and 60 visits

in India. Patients allocated to the health facility DOT would need to make these visits in person. Results are in table S4 and show that the SOC would still be the most expensive strategy in all cases.

Results of the probabilistic sensitivity analysis are in table S5.

7 SUPPLEMENTARY TABLES AND FIGURES

Table S1. STREAM unit costs used in calculating health system costs.

Cost category	Ethiopia (US$)	India (US$)	Uganda (US$)
Overheads per visit	0.02	0.01	0.01
Sputum culture	7.4	2.5	5.6
Sputum smear	7.2	5.8	16.6
ALT per test	17.3	9.4	15.4
AST per test			
Serum Creatinine per test			12.6
Serum Potassium per test			
Full Blood Count	3.3		4.2
ECG per test	2.7	1.6	14
TSH&thyroxine of free thyroxine	5.7	5.6	14
Chest X-ray	7.4	2	8.4
N95 for healthcare worker per item	1.6	2.1	1.3
Surgical mask for patients per item	0.1	0.1	0.04
Surgical gloves per pair	0.3	0.3	0.03

Table S2. Unit costs used in the analysis that were tested in the probabilistic sensitivity analysis

	Ethiopia			India			Uganda			
Cost category	Cost (US$)	95% credible interval	Source	Cost (US$)	95% credible interval	Source	Cost (US$)	95% credible interval	Source	Distribution
Internet nurse per visit	0.04	(0.03, 0.06)	[11]	0.4	(0.3, 0.5)	[15]	0.3	(0.2, 0.4)	[17]	gamma
Internet patient per visit	0.2	(0.2, 0.3)	[11]	0.6	(0.4, 0.7)	[15]	1.1	(0.8, 1.5)	[17]	gamma
Smartphone cost	234.0	(163.8, 304.2)	[12]	107.3	(75.1, 139.4)	[16]	155.3	(108.7, 201.9)	[17]	gamma
Renting toll free line per treatment duration	0.03	(0.02, 0.04)	[13]	0.03	(0.02, 0.04)	[13]	0.03	(0.02, 0.04)	[13]	gamma
Envelopes costs	2.58	(1.81, 3.35)	[13]	2.58	(1.81, 3.35)	[13]	2.58	(1.81, 3.35)	[13]	gamma
SMS and call costs	2.73	(1.91, 3.55)	[13]	2.73	(1.91, 3.55)	[13]	2.73	(1.91, 3.55)	[13]	gamma

Cost of labor to wrap medication	0.22	(0.15, 0.29)	[13]	0.22	(0.15, 0.29)	[13]	0.22	(0.15, 0.29)	[13]	gamma
Indirect cost patient/DOT supervisor per minute	0.01	(0.00, 0.01)	[14]	0.01	(0.01, 0.02)	[14]	0.01	(0.00, 0.01)	[14]	gamma
Staff cost per minute	0.01	(0.01, 0.01)	[14]	0.05	(0.04, 0.07)	[14]	0.06	(0.04, 0.08)	[14]	gamma

Table S3. Scenario analysis where smartphone costs were eliminated from the health system costs

	Ethiopia	**India**	**Uganda**
VOT in base case	3999.917	2201.7	6716.74
VOT in scenario analysis	3844.922	2140.491	6607.643
SOC DOT base case	3790.36	2003.26	6348.56

Table S4. Scenario analysis for a 6-month all-oral regimen

	India (US$)			**Ethiopia (US$)**			**Uganda (US$)**		
	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	1965.72	198.51	2164.23	3773.54	350.49	4,124.03	6246.88	544.21	6791.09
VOT	2108.06	22.67	2130.73	3965.02	17.87	3,982.88	6517.53	27.74	6545.27
99DOTS	1956.28	22.11	1978.39	3769.34	17.90	3,787.24	6141.06	27.43	6168.49
Family-observed	1968.79	31.76	2000.55	3765.41	26.33	3,791.74	5974.96	29.48	6004.44

Table S5. Probabilistic sensitivity analysis results

	Ethiopia (US$)			**India (US$)**			**Uganda (US$)**		
	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3732.41	570.16	4362.62	1899.26	322.95	2327.41	6095.52	885.29	7237.13
VOT	3901.62	17.80	3919.42	1997.39	22.59	2019.98	6499.54	27.61	6749.48
99DOTS	3754.11	17.83	3771.94	1912.85	22.03	1934.88	6121.71	27.33	6183.73
Family-observed	3748.61	6.49	3755.11	1907.52	20.83	1928.35	5937.23	16.32	6009.49

Table S6. Deterministic sensitivity analysis on LTFU and relapse rates for the digitally-observed and family-observed DOT

a) A 5% LTFU rate was tested

	Ethiopia (US$)			India (US$)			Uganda (US$)		
LTFU- 5%	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3790.4	572.3	4362.6	2003.3	324.1	2327.4	6348.6	888.6	7237.1
VOT	3996.6	17.9	4014.5	2200.1	22.7	2222.8	6711.2	27.7	6738.9
99DOTS	3766.2	17.9	3784.0	1978.7	22.1	2000.8	6146.0	27.4	6173.4
Family-observed	3762.2	26.3	3788.5	2003.3	31.7	2035.0	5977.4	29.5	6006.9

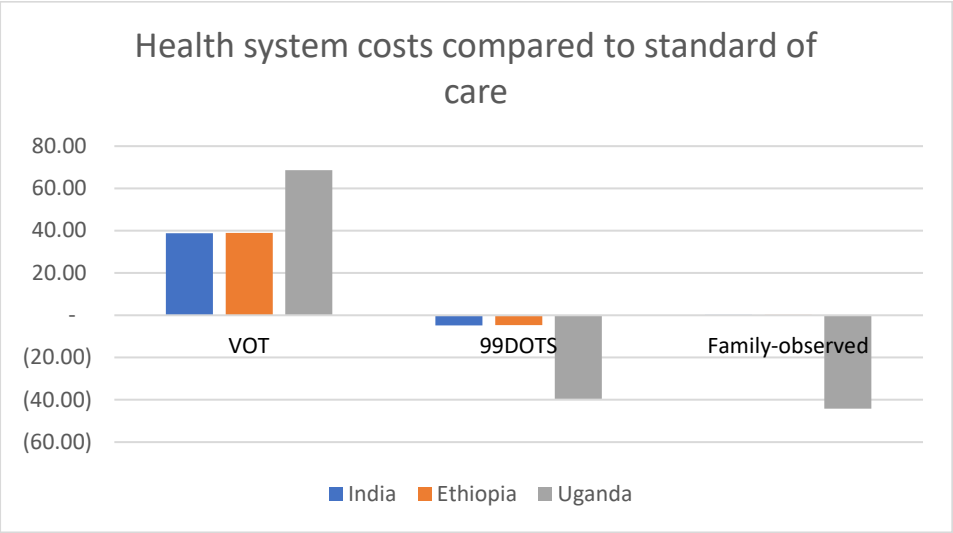
b) A 10% LTFU rate was tested

	Ethiopia (US$)			India (US$)			Uganda (US$)		
LTFU- 10%	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3790.4	572.3	4362.6	2003.3	324.1	2327.4	6348.6	888.6	7237.1
VOT	3993.3	17.8	4011.2	2198.6	22.6	2221.2	6705.7	27.7	6733.4
99DOTS	3763.0	17.9	3780.8	1977.1	22.1	1999.1	6140.8	27.4	6168.2
Family-observed	3759.1	26.3	3785.3	2001.6	31.7	2033.3	5974.9	29.4	6004.3

c) A 6.5% relapse rate

	Ethiopia (US$)			India (US$)			Uganda (US$)		
Relapse 6.5%	Health system	Patient	Societal	Health system	Patient	Societal	Health system	Patient	Societal
SOC	3790.4	572.3	4362.6	2003.3	324.1	2327.4	6348.6	888.6	7237.1
VOT	4002.9	17.9	4020.8	2203.3	22.7	2226.0	6721.7	27.8	6749.5
99DOTS	3772.4	17.9	3790.4	1982.0	22.1	2004.2	6156.3	27.5	6183.7
Family-observed	3768.5	26.4	3794.9	2006.6	31.8	2038.4	5980.0	29.5	6009.5

Figure S1. Health system costs compared to standard of care for each of VOT, 99DOTS and family-observed DOT, in each country



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3. Participant questionnaires used in paper 1 and paper 3

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: D D M M M Y Y Y Y (2 0 1)

Patient's Initials:

Study Number: X

Week Number:

PATIENT CONSENT SECTION

The questions on this form are about the patient's social and economic situation and are part of the assessment of patient costs of treatment and the impact of MDR-TB on their life.

Is the patient still willing to provide information on their treatment costs?… Yes ☐ No ☐

If 'No', please do not continue with the rest of this form.

TREATMENT COSTS (since previous interview) SECTION

Costs relating to DOTs

1a. Current patient status: ☐ Treatment phase (**go to Q1b**) ☐ Follow-up phase **(go to Q36)**

1b. Does patient receive DOTs at home?…… Yes ☐ No ☐ **If Yes, go to question 9**

2. Where do you currently take your MDR TB drugs?

If the patient has visited two different DOT places, tick the current place and report costs only for that place.

Public Health Facility/hospital …… ☐ Community ☐ Dispensary ☐

Private Health Facility/hospital…… ☐ Workplace ☐

3. How many times a week do you go there to take your drugs? (select one answer)

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

4. Who watches over your drugs? (select one answer)

Clinical Officer ☐ Nurse…… ☐ Other Clinic Employee…… ☐ Community Healthcare worker ☐

Family member ☐ Self/no one ☐ Other community worker ☐

5. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

6. How long does one of these visits take on average, including time on the road and waiting time? (total turn around time)……minutes

7. From your home to the DOT place, how much does it cost if you take transport (both ways)?

……

8. If you need to buy food (e.g. lunch), how much do you spend on food while travelling or waiting?

……

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: D D M M M 2 0 1 Y Y Y Y

Patient's Initials:

Study Number: X

Week Number:

TREATMENT COSTS SECTION continued...

Costs relating to DOTs - MDR TB injections

9. Does the patient receive MDR-TB injections? Yes ☐ No ☐ **If No, go to question 19**

10. Does the patient receive MDR-TB injections at an alternative location to their other MDR-TB drugs?

Yes ☐ No ☐ **If No, go to question 19**

11. Where do you currently receive your MDR TB injections?

If the patient has visited two different DOT places, tick the current place and report costs only for that place.

Public Health Facility/hospital ☐ Community ☐ Dispensary…… ☐

Private Health Facility/hospital ☐ Workplace… ☐ Home…… ☐

12. How many times a week do you go there to receive MDR TB injections?

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

13. Who watches over your injectable drugs? (select one answer)

Clinical Officer ☐ Nurse…… ☐ Other Clinic Employee…… ☐ Community Healthcare worker ☐

Family member ☐ Self/no one ☐ Other community worker ☐

14. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

15. How long does one of these visits take on average, including time on the road and waiting time?
(total turn around time)……minutes

16. From your home to the DOT place, how much does it cost if you take transport (both ways)?

……

17. If you need to buy food (e.g. lunch), how much do you spend on food while travelling or waiting?

……

18. **a)** Do you have to pay administration fees when you go to receive your MDR-TB injections?

Yes ☐ No ☐

b) If yes, how much? ……

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

TREATMENT COSTS SECTION continued...

Costs related to picking up the MDR TB drugs - where drugs are <u>currently</u> picked up.

19. Is patient still in treatment phase? Yes [ ] No [ ] **<u>If No, go to question 36</u>**

20. Does patient pick up their drugs during the scheduled patient assessment visits at the treating clinic?

Yes [ ] No [ ] **<u>If No go to question 28</u>**

21. How often do you travel to the health facility / hospital for picking up your MDR TB drugs?

[ ][ ] Times/month

22. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: …….

23. How long does one of these visits take on average, including time on the road and waiting time? (total turn around time)……minutes

24. From your home to the facility, how much does it cost if you take transport (both ways)?

……

25. If you go to the facility to pick up your drugs, how much do you spend on food on that day (on the road, while waiting for lunch etc)?

……

26. **a)** Do you have to pay administration fees when picking up your MDR TB drugs?

Yes [ ] No [ ]

b) If yes, how much? ……

27. **a)** Do you have any accommodation costs when picking up your MDR TB drugs?

Yes [ ] No [ ]

b) If yes, how much? ……

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: D D M M M 2 0 1 Y Y Y Y

Patient's Initials:

Study Number: X

Week Number:

TREATMENT COSTS SECTION continued…

Costs related to scheduled patient assessment visits

28. Is the patient currently in the treatment phase?

Yes ☐ No ☐ **If No, go to question 36**

29. How long does it take you to get to the health facility (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

30. How long does one of these visits take on average, including time on the road and waiting time?
(total turn around time)……minutes

31. From your home to the facility, how much does it cost if you take transport (both ways)?

……

32. If you go to the facility to pick up your drugs, how much do you spend on food on that day (on the road, while waiting for lunch etc)?.....

33. **a)** Do you have to pay administration fees when you attend for an assessment visit?

Yes ☐ No ☐

b) If yes, how much?: ……

34. **a)** Do you have any accommodation costs when attending assessment visits?

Yes ☐ No ☐

b) If yes, how much?: ……

35. **a)** Since the beginning of treatment or since the last time of asking, have you ever had to go to the health facility in addition to your scheduled visits for follow up tests?

Yes ☐ No ☐ **If No, go to question 45**

b) How long does one of these assessment visits take on average, including time on the road, waiting time and tests (total turnaround time)?……minutes

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

TREATMENT COSTS SECTION continued...

Costs related to scheduled follow-up visits.

36. Is the patient currently in the follow-up phase?

Yes [ ] No [ ] **If No, go to question 45**

37. Does the location for follow-up visits differ from that during the treatment phase?

Yes [ ] No [ ] **If No, go to question 44**

38. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

39. How long does one of these visits take on average, including time on the road and waiting time?

(total turn around time)……minutes

40. From your home to the facility, how much does it cost if you take transport (both ways)?

……

41. If you go to the facility for follow-up, how much do you spend on food on that day (on the road, while waiting for lunch etc)?

……

42. **a)** Do you have to pay administration fees when you attend for a follow-up visit?

Yes [ ] No [ ]

b) If yes, how much? ……

43. **a)** Do you have any accommodation costs when attending follow-up visits?

Yes [ ] No [ ]

b) If yes, how much? ……

44. **a)** Since the last time of asking, have you ever have to go to the health facility in addition to your scheduled visits for follow up tests since the beginning of treatment?

Yes [ ] No [ ]

b) How long does one of these follow-up visits take on average, including time on the road, waiting time and tests (total turnaround time)?……minutes

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

GUARDIAN COSTS (since previous interview) SECTION

45. Does any family/friend/DOT supporter accompany you on any visits or go in your place to collect your MDR TB drugs?

Yes [ ] No [ ] **If No, go to question 51**

46. On how many visits has your family/friend/DOT supporter accompanied you or gone in your place

a) For scheduled visits for MDR TB assessment/follow up? [ ][ ] times

b) For unscheduled visits to any health care facility? [ ][ ] times

47. How much does your supporter spend on scheduled visits for MDR TB assessment/follow up on:

a) Transport:…… **b)** Food:……

c) Accommodation:…… **d)** Total Costs:……

48. How much does your supporter spend on unscheduled visits to any health care facility on:

a) Transport:…… **b)** Food:……

c) Accommodation:…… **d)** Total Costs:……

49. **a)** Does your friend/family/DOT supporter have an income? Yes [ ] No [ ]

b) If yes, how much per day?……

50. **a)** Why did someone accompany you?

Administrative barriers…… [ ] Distance [ ] Security [ ] Too ill to travel alone [ ]

Was required for treatment [ ] Other [ ]

b) If Other, specify why:……

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: ☐☐ ☐☐☐ 2☐1☐ (D D M M M Y Y Y Y)

Patient's Initials: ☐☐☐

Study Number: ☐☐☐☐☐☐X

Week Number: ☐☐☐

HOSPITALISATION SECTION

51. **a)** Is this the first post-enrolment interview? Yes ☐ No ☐ **If No, go to question 52**

b) Were you hospitalized at post-enrolment period? Yes ☐ No ☐ **If Yes, go to question 53** **If No, go to question 55**

52. **a)** Since the previous interview have you been hospitalised again for your MDR TB Treatment?

Yes ☐ No ☐ **If No, go to question 55**

b) How many days in total did you stay at the hospital? ☐☐☐ Days

c) How much did you pay in the hospital during your entire stay? (If nothing was spent, enter 0)

i) Total Cost:…… **ii)** Hospital Administration Fees Cost:……

iii) Sheets/Linen Cost:…… **iv)** Food Cost:……

v) Transport Cost: …… **vi)** Drugs: Cost:……

vii) Other Cost:……

d) If Other Cost, specify what:……

53. **a)** Did any family/friend stay with you while in hospital? Yes ☐ No ☐ **If No, go to question 54**

b) How many days in total did family/friend stay with you (sleep there)? ☐☐☐ Days

c) How much did your relative/friend pay for staying in the hospital? (enter 0 If nothing spent)

i) Total Cost: …… **ii)** Accommodation Cost: ……

iii) Food: Cost:…… **iv)** Transport Cost:……

v) Other Cost: ……

d) If Other Cost, specify what: ……

e) Does your friend/family/DOT supporter have an income? Yes ☐ No ☐

f) If Yes, how much per day?……

54. **a)** Did any other family/friend visit you while you were in hospital?

Yes ☐ No ☐ **If No, go to question 55**

b) If Yes, how many people visited you? ☐☐☐ Persons

c) How many times did they visit you? ☐☐☐ Times

d) What were the costs for your relative/friend who stayed with you in the hospital most recently? (If nothing was spent, enter ***0***)

i) Total Cost: …… **ii)** Accommodation Cost: ……

iii) Food: Cost:…… **iv)** Transport: Cost: ……

v) Other Cost: ……

e) If Other Cost, specify what:……

f) How long were the visits including travelling time? ……hours……minutes

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

OTHER COSTS (since previous interview) SECTION

Food Supplements

55. **a)** Do you (or others – e.g. family members) buy any supplements for your diet because of the MDR TB illness, for example vitamins, meat, energy drinks, soft drinks, fruits or medicines?

Yes [ ] No [ ]

b) If Yes, what kind of items?

i) Fruits:……Yes [ ] No [ ] **ii)** Drinks:……Yes [ ] No [ ] **iii)** Vitamins/herbs:……Yes [ ] No [ ]

iv) Meat: … Yes [ ] No [ ] **v)** Other: ……Yes [ ] No [ ]

c) If Other, specify:……

d) How much did you spend on these items approximately?……

Illnesses

56. **a)** Do you have any chronic illnesses for which you are receiving treatment?

Yes [ ] No [ ] **<u>If No, go to question 57</u>**

b) What is/are the illness (es)?……

c) Are there any additional costs for your household because of this other illness besides the costs that you have already mentioned? Yes [ ] No [ ]

d) If Yes, what were the costs? (If nothing was spent, enter 0)

i) Total Cost: …… **ii)** Tests Cost:……

iii) Drugs Cost:…… **iv)** Transport Cost:……

v) Food Cost:…… **vi)** Other Cost: ……

e) If Other Cost, specify what:……

57. **a)** How much was spent on your healthcare (by you, your household or other family member) on average per month BEFORE the MDR TB illness?……

b) How much is spent on your healthcare (by you, your household or other family member) on average per month NOW?……

Insurance

58. **a)** Do you have any kind of private or government health/medical insurance scheme?

Yes [ ] No [ ]

b) If Yes, what insurance scheme?

i) Reimbursement Scheme: Yes [ ] No [ ] **ii)** Monthly medical allowance:…… Yes [ ] No [ ]

iii) Family/community fund: Yes [ ] No [ ] **iv)** Western Scheme (contract): …… Yes [ ] No [ ]

v) Other:…… Yes [ ] No [ ]

c) If Other, specify:……

STREAM 1
Patient Treatment and Follow Up Costs

Visit Date: D D M M M 2 0 1 Y Y Y Y

Patient's Initials:

Study Number: X

Week Number:

OTHER COSTS SECTION continued...

Coping Costs

59. **a)** Did you borrow any money to cover costs due to the MDR TB illness since the last inter view?

Yes ☐ No ☐ **If No, go to question 60**

b) If Yes, how much did you borrow?..... **c)** When? D D M M M 2 0 1 Y Y Y Y

d) From whom did you borrow?

i) Family: ..... Yes ☐ No ☐ **ii)** Neighbours/friends:... Yes ☐ No ☐

iii) Private Bank: .... Yes ☐ No ☐ **iv)** Cooperative:.....Yes ☐ No ☐

v) Other: ....Yes ☐ No ☐

e) If Other, specify:.....

f) What is the duration of the loan?.....Weeks .....Months ..... Years (single answer)

g) Please indicate the intervals at which repayments are to be made:

Weekly: ☐ Monthly: ☐ Annually: ☐ I am not expected to pay the money back ☐

Other: ☐ **h)** If Other, specify:.....

i) What is the interest rate on the loan? (%)

Less than 10: ☐ 10 to 15: ☐ More than 15: ☐ I don't pay interest: ☐

60. **a)** Have you sold any of your property to finance the cost of the MDR TB illness? Yes ☐ No ☐

b) If Yes, what did you sell?

i) Land: ..... Yes ☐ No ☐ **ii)** Livestock: ..... Yes ☐ No ☐

iii) Transport/vehicle: Yes ☐ No ☐ **iv)** Household item: Yes ☐ No ☐

v) Farm Produce: ..... Yes ☐ No ☐ **vi)** Other: .....Yes ☐ No ☐

c) If Other, specify:.....

d) What is the estimated market value of the property you sold?:.....

e) How much did you earn from the sale of your property?:.....

Signature:	Printed Name:	Date CRF Completed: D D M M M 2 0 Y Y Y Y
Signature:	Printed Name:	Date CRF Verified: D D M M M 2 0 Y Y Y Y

Date of first database entry: D D M M M 2 0 Y Y Y Y Initials of data entry officer:

Date of second database entry: D D M M M 2 0 Y Y Y Y Initials of data entry officer:

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: D D M M M Y Y Y Y (2 0 1)

Patient's Initials:

Study Number: X

INDIVIDUAL SITUATION AND INCOME SECTION

Primary Earner

1. **a)** Who is usually the primary income earner in the household? ***(tick one box only)***

Wife/mother/partner……. ☐ Husband/Father/Partner ☐ Patient…… ☐

Son/daughter …… ☐ Extended family ☐ Other…… ☐

b) If Other, specify:……

Education

2. **a)** What is the highest level of education of the patient?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other…… ☐

b) If Other, specify:……

3. **a)** What is the highest level of education of the primary income earner?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other …… ☐

b) If Other, specify:……

4. **a)** What is the highest level of education of the Head of the Household?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other …… ☐

b) If Other, specify:……

5. **a)** What is the highest level of education of the Spouse of the Head of the Household?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know …… ☐ Other …… ☐

N/A…… ☐

b) If Other, specify:……

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: D D M M M Y Y Y Y (2 0 1) | Patient's Initials: | Study Number: X

INDIVIDUAL SITUATION AND INCOME SECTION continued...

Employment and family

6. **a)** Are you currently formally employed?

Yes, formal work	(go to 13)	No, informal work	(go to 13)
On sick leave	(go to 7)	Retired	(go to 11)
School, university	(go to 16)	Housework	(go to 13)
No, not working	(go to 7)	Other	(go to 6b)

b) If Other, specify:……

7. **a)** Is the reason for not working related to the illness that led to your enrolment in the trial?

Yes ☐ No ☐

b) If Yes, when was the last time you were working? D D M M M Y Y Y Y (2 0 1)

8. Did you become financially dependent on somebody because of illness? Yes ☐ No ☐

9. **a)** Have you ever stopped working/going to school/doing housework due to the illness that led to enrolment in the trial?

Yes ☐ No ☐

b) If Yes, for how long?

Less than 1 month ☐ One month ☐ 2-3 months ☐ 4-5 months ☐
More than 6 months ☐

10. **a)** Does someone stay home specifically to take care of you because of your illness? Yes ☐ No ☐

b) If Yes, for how long? ☐☐ Weeks

c) If Yes, did they quit their income-earning job to stay home and care for you?…… Yes ☐ No ☐

11. **a)** How regularly did you work before you became ill with the illness that led to enrolment in the trial?

Throughout the year ☐ Seasonal/part of the year ☐ Day labour ☐ Other ☐

b) If Other, specify:……

12. Did you have to change jobs when you became ill with the illness that led to enrolment in the trial?

Yes ☐ No ☐

13. **a)** What is your main occupation?

Sales/service… ☐ Agriculture… ☐ Household duties… ☐ Production/construction… ☐
Other…… ☐

b) If Other, specify:……

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: D D M M M 2 0 1 Y | Patient's Initials: | | | | Study Number: X

INDIVIDUAL SITUATION AND INCOME SECTION continued…

14. **a)** How are you usually paid?

Cash ☐ In kind ☐ Not paid ☐ Bank transferred salary ☐ Other ☐

b) If Other, Specify:……

15. **a)** How are you usually paid? Per day ☐ Per month ☐ Don't earn ☐

b) What was your estimated personal take home earning BEFORE the illness that led to enrollment in the trial? (includes welfare, disability, or other social support)……

c) Are you a housewife? Yes ☐ No ☐ **<u>If Yes, go to question 16</u>**

d) What is your estimated personal take home earning NOW? (includes welfare, disability, or other so cial support) ……

e) Don't earn? Yes ☐ No ☐

f) *If answer to 15d differs from 15b,* is the change related to the illness that led to enrolment in the trial? Yes ☐ No ☐

16. **a)** How many hours did you work/study on average per day BEFORE you became ill with the illness that led to enrolment in the trial? ☐☐ Hours

b) How many hours do you work/study on average NOW per day? ☐☐ Hours

c) *If answer to 16a differs from 16b,* is the change related to the illness that led to enrolment in the trial?

Yes ☐ No ☐

d) *If answer to 16a differs from 16b,* is someone doing the work that you used to do?

Yes ☐ No ☐

e) If Yes: **i)** Daughter: Yes ☐ No ☐ **ii)** Son…… Yes ☐ No ☐ **iii)** Spouse: Yes ☐ No ☐

iv) Friend…… Yes ☐ No ☐ **v)** Other Family. Yes ☐ No ☐

17. **a)** Do you have children of or below school age? Yes ☐ No ☐ **<u>If No, go to question 18</u>**

b) Do all of your children of school age attend school regularly? Yes ☐ No ☐

c) If No, why not?

i) Needs to help around the house…Yes ☐ No ☐ **ii)** No money for school fees… Yes ☐ No ☐

iii) Has to work to earn income……Yes ☐ No ☐ **iv)** Also sick……Yes ☐ No ☐

v) Other……Yes ☐ No ☐

d) If Other, specify:……

e) Do any of your children of or below school age work to finance costs due to the illness that led to en rolment in the trial: Yes ☐ No ☐

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y) Patient's Initials: [ ][ ][ ] Study Number: [ ][ ][ ][ ][ ][ ][X]

INDIVIDUAL SITUATION AND INCOME SECTION continued...

18. Imagine if you employed someone to do the housework for your household, how much would you have to pay him/her per month?
Ai) While you are sick …… **Aii)** Don't know [ ]
Bi) While you are healthy:…… **Bii**) Don't know [ ]

19. **a)** Has the illness that led to your enrolment affected your social or private life in any way?
Yes [ ] No [ ] **<u>If No, go to question 20</u>**

b) If Yes, how?
i) Loss of job…Yes [ ] No [ ] **ii)** Dropped out of school…… Yes [ ] No [ ]
iii) Divorce…… Yes [ ] No [ ] **iv)** Separated from spouse/partner …Yes [ ] No [ ]
v) Sick child… Yes [ ] No [ ] **vi)** Disruption of sexual life…… Yes [ ] No [ ]
vii) Other……Yes [ ] No [ ]

c) If Other, specify:……

d) Has this resulted in a financial burden? Yes [ ] No [ ]

20. How much was spent on your healthcare (by you, your household or other family member) on average per month BEFORE the illness that led to enrolment in the trial:……

21. **a)** What is your ethnicity?……

b) What is your religion? ……

HOUSEHOLD STRUCTURE AND COSTS SECTION

Residents

22. How many people regularly sleep in your house? (including patient): [ ][ ] persons
If patient lives alone, go to section B and replace the word 'household' with 'you'

23. How many of the household members are paid for working? (including patient)
(includes payment in kind or farm produce): [ ][ ] persons

24. **a)** Besides yourself, does anyone else of your household receive treatment for MDR TB?
Yes [ ] No [ ]
b) If Yes, how many? [ ][ ] persons

Food Consumption

25. What is the proportion of the total food consumed every month that:
a) Was purchased? ……
b) Was produced at home?……

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

HOUSEHOLD STRUCTURE AND COSTS SECTION continued…

26. **a)** How much food did your household purchase every month on average BEFORE the illness that led to enrolment in the trial? Total Cost:……

b) If the food that you produced at home per month BEFORE the illness that led to enrolment in the trial was sold on the market, how much would it be worth? Total Cost:……

c) How much food does your household purchase NOW every month on average? Total Cost:……

d) If the food that you produce at home per month NOW was sold on the market, how much would it be worth? Total Cost:……

e) If answer to 26a differs from 26c, has the amount of food consumed per month changed due to the illness that led to enrolment in the trial? Yes ☐ No ☐

SOCIOECONOMIC INDICATORS SECTION

27. What is your electricity supply?
Own Connection ☐ Shared Connection ☐ None ☐

28. What is your source of drinking water? (Choose one answer)
Lake/pond/dam/river ☐ Protected well… ☐ Bore hole …… ☐ Unprotected spring ☐
Piped into dwelling…… ☐ Piped into yard ☐ Public tap/standpipe ☐

29. How many rooms are there in your house?
1 Room ☐ 2 Rooms ☐ 3 Rooms ☐ 4 Rooms ☐ More than 4 ☐

30. **a)** Current place of residence? (*in Amharic version Urban slum is deleted)*
Urban ☐ Urban Slum ☐ Rural ☐ Other ☐

b) If Other, specify:……

31. Do you own the house of residence you live in? Yes ☐ No ☐

32. **a)** What power do you use for cooking most frequently? (Choose one answer)
Own electricity connection …… ☐ Shared electricity connection ☐ Gas… ☐ Paraffin ☐
Charcoal or purchased firewood ☐ Collected firewood …… ☐ Other ☐

b) If Other, specify:……

STREAM 1
Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

SOCIOECONOMIC INDICATORS SECTION continued...

33. **a)** Where is your place for cooking? (Choose one answer)

In the house [ ] In a separate building [ ] Outdoors [ ] No food is cooked in the house [ ]

Other..... [ ]

b) If Other, specify:.....

34. **a)** What is the floor in your house made from? (Choose one answer)

Earth/sand [ ] Dung [ ] vinyl/asphalt [ ] Cement [ ] Other [ ]

b) If Other, specify:.....

35. **a)** Do you own:

i) Radio ..... Yes [ ] No [ ]
ii) Mobile phone..... Yes [ ] No [ ]
iii) Television..... Yes [ ] No [ ]
iv) Non-mobile phone ..... Yes [ ] No [ ]
v) Refrigerator..... Yes [ ] No [ ]
vi) Bicycle ..... Yes [ ] No [ ]
vii) Animal-drawn cart.....Yes [ ] No [ ]
viii) Motorcycle/Scooter..... Yes [ ] No [ ]
ix) Car/truck.....Yes [ ] No [ ]
x) Livestock (farm animals)..... Yes [ ] No [ ]
xi) Land..... Yes [ ] No [ ]

b) If you own land, quantify:.....

36. **a)** If the government could provide you with some service to ease the burden of the illness that led to enrolment in the trial on you and your household, what would you prefer to have?

i) Transport Vouchers..... Yes [ ] No [ ]
ii) Food vouchers..... Yes [ ] No [ ]
iii) More efficient service... Yes [ ] No [ ]
iv) Housing support..... Yes [ ] No [ ]
v) Other..... Yes [ ] No [ ]

b) If Other, please explain some more:.....

Thank you for your cooperation! Is there anything you would like to ask or say?
.....

Signature:	Printed Name:	Date CRF Completed: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)
Signature:	Printed Name:	Date CRF Verified: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

Date of first database entry: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y) Initials of data entry officer: [ ][ ][ ]

Date of second database entry: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y) Initials of data entry officer: [ ][ ][ ]

STREAM 1
Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)
Patient's Initials: [ ][ ][ ]
Study Number: [ ][ ][ ][ ][ ][ ][X]
Week Number: [ ][ ][ ]

PATIENT CONSENT SECTION

The questions on this form are about the patient's social and economic situation and are part of the assessment of patient costs of treatment and the impact of MDR-TB on their life.

Is the patient still willing to provide information on their socioeconomic status? Yes [ ] No [ ]

If 'No', please do not continue with the rest of this form.

INDIVIDUAL SITUATION AND INCOME SECTION

Employment and family

1. **a)** Are you currently formally employed? (***tick one box only***)

Yes, formal work [ ] (go to 5) No, informal work [ ] (go to 5) On sick leave [ ] (go to 2)
Retired [ ] (go to 2) School, university [ ] (go to 8) Housework [ ] (go to 3)
No, not working [ ] (go to 2) Other [ ] (go to 1b)

b) If Other, specify:……

2. **a)** Is the reason for not working related to the illness that led to your enrolment in the trial?

Yes [ ] No [ ]

b) If Yes, when was the last time you were working? [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

3. Are you financially dependent on somebody because of illness?…… Yes [ ] No [ ]

4. **a)** Does someone stay home specifically to take care of you?…… Yes [ ] No [ ]

b) If yes, for how long? [ ][ ] Weeks

c) Did they quit their income-earning job to stay home and care for you?… Yes [ ] No [ ]

5. **a)** What is your main occupation?:

Sales/service [ ] Agriculture [ ] Household [ ] Production/construction [ ] Other [ ]

b) If Other, specify:……

6. **a)** How are you usually paid?

Cash [ ] In kind [ ] Not paid [ ] Bank transferred salary [ ] Other [ ]

b) If Other, specify:……

7. **a)** How are you usually paid? Per day [ ] Per month [ ] Don't earn [ ]

b) What is your estimated personal take home earning NOW (includes welfare, disability, or other social support):……

c) Are you a housewife? Yes [ ] No [ ]

STREAM 1
Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

INDIVIDUAL SITUATION AND INCOME SECTION continued...

8. How many hours do you work/study on average NOW per day? [ ][ ] Hours

9. **a)** Do you have children of or below school age? Yes [ ] No [ ] **If No, go to question 10**

b) Do all of your children of school age attend school regularly? Yes [ ] No [ ]

c) If No, why not?

i) Needs to help around the house: Yes [ ] No [ ] **ii)** No money for school fees:.....Yes [ ] No [ ]

iii) Has to work to earn income:..... Yes [ ] No [ ] **Iv)** Also sick:..... Yes [ ] No [ ]

v) Other: ..... Yes [ ] No [ ]

d) If Other, specify:.....

e) Do any of your children of or below school age work to finance costs due to the illness that led to enrolment in the trial: Yes [ ] No [ ]

10. Imagine if you employed someone to do the housework for your household, how much would you have to pay him/her per month? **Ai)** While you are sick: ..... **Aii)** Don't know [ ]

Bi) While you are healthy:..... **Bii)** Don't know [ ]

11. **a)** Has the illness that led to your enrolment affected your social or private life in any way?

Yes [ ] No [ ] **If No, go to question 12**

b) If Yes, how?

i) Loss of job:..... Yes [ ] No [ ] **ii)** Dropped out of school:..... Yes [ ] No [ ]

iii) Divorce:.....Yes [ ] No [ ] **iv)** Separated from spouse/partner:... Yes [ ] No [ ]

v) Sick child:..... Yes [ ] No [ ] **vi)** Disruption of sexual life:..... Yes [ ] No [ ]

vii) Other..... ..... Yes [ ] No [ ]

c) If Other, specify:.....

d) Has this resulted in a financial burden?..... Yes [ ] No [ ]

12. **a)** Do you receive any of these services to ease the burden of the illness that led to enrolment in the trial?

i) Transport Vouchers:..... Yes [ ] No [ ] **ii)** Food vouchers:.....Yes [ ] No [ ]

iii) Housing support :.....Yes [ ] No [ ] **iv)** Other :..... Yes [ ] No [ ]

b) If Other, specify:.....

STREAM 1
Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][1][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

HOUSEHOLD STRUCTURE AND COSTS SECTION

Residents

13. How many people regularly sleep in your house? (including patient) [ ][ ] persons

If patient lives alone, go to question 16 and replace the word 'household' with 'you'.

14. How many of the household members are paid for working? (including patient)

(includes payment in kind or farm produce):…… [ ][ ] persons

15. **a)** Besides yourself, does anyone else of your household receive treatment for MDR TB?

Yes [ ] No [ ]

b) If yes, how many people? …… [ ][ ] persons

Food Consumption

16. What is the proportion of the total food every month that:

ai) Was purchased? …… **aii)** Was produced at home?……

b) How much food does your household purchase NOW every month, on average? Total Cost:……

c) If the food that you produced at home per month NOW was sold on the market, how much would it be worth? Total Cost:……

SOCIOECONOMIC INDICATORS SECTION

17. What is your electricity supply?

Own Connection [ ] Shared Connection [ ] None [ ]

18. What is your source of drinking water? (Choose one answer)

Lake/pond/dam/river [ ] Protected well… [ ] Bore hole …… [ ] Unprotected spring [ ]

Piped into dwelling…… [ ] Piped into yard [ ] Public tap/standpipe [ ]

19. How many rooms are there in your house?

1 Room…… [ ] 2 Rooms [ ] 3 Rooms [ ] 4 Rooms [ ] More than 4 [ ]

20. **a)** Current place of residence? (Urban slum is deleted in Amharic version)

Urban…… [ ] Urban Slum [ ] Rural [ ] Other [ ]

b) If Other, specify:……

c) Do you own the house or residence you live in? Yes [ ] No [ ]

STREAM 1
Patient Socio-economic Status: Generic

Visit Date: D D M M M 2 0 1 Y Y Y Y

Patient's Initials:

Study Number: X

Week Number:

SOCIOECONOMIC INDICATORS SECTION continued...

21. **a)** What power do you use for cooking most frequently? (Choose one answer)

Own electricity connection ..... Shared electricity connection Gas... Paraffin

Charcoal or purchased firewood Collected firewood..... Other

b) If 'Other', please specify:.....

c) Where is your place for cooking? (Choose one answer)

In the house In a separate building Outdoors No food is cooked in the house

Other.....

d) If Other, specify:.....

22. **a)** What is the floor in your house made from? (Choose one answer)

Earth/sand Dung Vinyl/asphalt Cement Other

b) If Other, specify:.....

23. **a)** Do you own:

i) Radio..... Yes No **ii)** Mobile phone..... Yes No

iii) Television..... Yes No **iv)** Non-mobile phone..... Yes No

v) Refrigerator..... Yes No **vi)** Bicycle..... Yes No

vii) Animal-drawn cart..... Yes No **viii)** Motorcycle/Scooter ..... Yes No

ix) Car/truck..... Yes No **x)** Livestock (farm animals): Yes No

xi) Land:..... Yes No

b) If you own land, please quantify:.....

Signature:	Printed Name:	Date CRF Completed: D D M M M 2 0 Y Y Y Y
Signature:	Printed Name:	Date CRF Verified: D D M M M 2 0 Y Y Y Y

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STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: ☐☐ ☐☐☐ 2 0 2 ☐ (D D M M M Y Y Y Y)

Patient's Initials: ☐☐☐

Study Number: ☐☐☐☐☐☐X

Week Number: ☐☐☐

PATIENT CONSENT SECTION

The questions on this form are about the patient's social and economic situation and are part of the assessment of patient costs of treatment and the impact of MDR-TB on their life.

Is the patient still willing to provide information on their treatment costs?… Yes ☐ No ☐

If 'No', please do not continue with the rest of this form.

TREATMENT COSTS (since previous interview) SECTION

Costs relating to DOTs

1a. Current patient status: ☐ Treatment phase (**go to Q1b**) ☐ Follow-up phase **(go to Q36)**

1b. Does patient receive DOTs at home?…… Yes ☐ No ☐ **If Yes, go to question 9**

2. Where do you currently take your MDR TB drugs?

If the patient has visited two different DOT places, tick the current place and report costs only for that place.

Public Health Facility/hospital …… ☐ Community ☐ Dispensary ☐

Private Health Facility/hospital…… ☐ Workplace ☐

3. How many times a week do you go there to take your drugs? (select one answer)

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

4. Who watches over your drugs? (select one answer)

Clinical Officer ☐ Nurse…… ☐ Other Clinic Employee…… ☐ Community Healthcare worker ☐

Family member ☐ Self/no one ☐ Other community worker ☐

5. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

6. How long does one of these visits take on average, including time on the road and waiting time? (total turn around time)……minutes

7. From your home to the DOT place, how much does it cost if you take transport (both ways)?

……

8. If you need to buy food (e.g. lunch), how much do you spend on food while travelling or waiting?

……

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: D D M M M Y Y Y Y (2 0 2)

Patient's Initials:

Study Number: X

Week Number:

TREATMENT COSTS SECTION continued...

Costs relating to DOTs - MDR TB injections

9. Does the patient receive MDR-TB injections? Yes ☐ No ☐ **If No, go to question 19**

10. Does the patient receive MDR-TB injections at an alternative location to their other MDR-TB drugs?

Yes ☐ No ☐ **If No, go to question 19**

11. Where do you currently receive your MDR TB injections?

If the patient has visited two different DOT places, tick the current place and report costs only for that place.

Public Health Facility/hospital ☐ Community ☐ Dispensary…… ☐

Private Health Facility/hospital ☐ Workplace… ☐ Home…… ☐

12. How many times a week do you go there to receive MDR TB injections?

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

13. Who watches over your injectable drugs? (select one answer)

Clinical Officer ☐ Nurse…… ☐ Other Clinic Employee…… ☐ Community Healthcare worker ☐

Family member ☐ Self/no one ☐ Other community worker ☐

14. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

15. How long does one of these visits take on average, including time on the road and waiting time?
(total turn around time)……minutes

16. From your home to the DOT place, how much does it cost if you take transport (both ways)?

……

17. If you need to buy food (e.g. lunch), how much do you spend on food while travelling or waiting?

……

18. **a)** Do you have to pay administration fees when you go to receive your MDR-TB injections?

Yes ☐ No ☐

b) If yes, how much? ……

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

TREATMENT COSTS SECTION continued…

Costs related to picking up the MDR TB drugs - where drugs are <u>currently</u> picked up.

19. Is patient still in treatment phase? Yes [ ] No [ ] **<u>If No, go to question 36</u>**

20. Does patient pick up their drugs during the scheduled patient assessment visits at the treating clinic?

Yes [ ] No [ ] Not applicable [ ] **<u>If Yes or Not applicable, go to question 28</u>**

21. How often do you travel to the health facility / hospital for picking up your MDR TB drugs?

[ ][ ] Times/month

22. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: …….

23. How long does one of these visits take on average, including time on the road and waiting time? (total turn around time)……minutes

24. From your home to the facility, how much does it cost if you take transport (both ways)?

……

25. If you go to the facility to pick up your drugs, how much do you spend on food on that day (on the road, while waiting for lunch etc)?

……

26. **a)** Do you have to pay administration fees when picking up your MDR TB drugs?

Yes [ ] No [ ]

b) If yes, how much? ……

27. **a)** Do you have any accommodation costs when picking up your MDR TB drugs?

Yes [ ] No [ ]

b) If yes, how much? ……

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

TREATMENT COSTS SECTION continued…

Costs related to scheduled patient assessment visits

28. Is the patient currently in the treatment phase?

Yes ☐ No ☐ **If No, go to question 36**

29. How long does it take you to get to the health facility (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

30. How long does one of these visits take on average, including time on the road and waiting time?
(total turn around time)……minutes

31. From your home to the facility, how much does it cost if you take transport (both ways)?

……

32. If you go to the facility to pick up your drugs, how much do you spend on food on that day (on the road, while waiting for lunch etc)?.....

33. **a)** Do you have to pay administration fees when you attend for an assessment visit?

Yes ☐ No ☐

b) If yes, how much?: ……

34. **a)** Do you have any accommodation costs when attending assessment visits?

Yes ☐ No ☐

b) If yes, how much?: ……

35. **a)** Since the beginning of treatment or since the last time of asking, have you ever had to go to the health facility in addition to your scheduled visits for follow up tests?

Yes ☐ No ☐ **If No, go to question 45**

b) How long does one of these assessment visits take on average, including time on the road, waiting time and tests (total turnaround time)?……minutes

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

TREATMENT COSTS SECTION continued...

Costs related to scheduled follow-up visits.

36. Is the patient currently in the follow-up phase?

Yes [ ] No [ ] **If No, go to question 45**

37. Does the location for follow-up visits differ from that during the treatment phase?

Yes [ ] No [ ] **If No, go to question 44**

38. How long does it take you to get there (one way)?

a) ……minutes walking and/or **b)** ……minutes with transport

c) Other: ……

39. How long does one of these visits take on average, including time on the road and waiting time?

(total turn around time)……minutes

40. From your home to the facility, how much does it cost if you take transport (both ways)?

……

41. If you go to the facility for follow-up, how much do you spend on food on that day (on the road, while waiting for lunch etc)?

……

42. **a)** Do you have to pay administration fees when you attend for a follow-up visit?

Yes [ ] No [ ]

b) If yes, how much? ……

43. **a)** Do you have any accommodation costs when attending follow-up visits?

Yes [ ] No [ ]

b) If yes, how much? ……

44. **a)** Since the last time of asking, have you ever have to go to the health facility in addition to your scheduled visits for follow up tests since the beginning of treatment?

Yes [ ] No [ ]

b) How long does one of these follow-up visits take on average, including time on the road, waiting time and tests (total turnaround time)?……minutes

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

GUARDIAN COSTS (since previous interview) SECTION

45. Does any family/friend/DOT supporter accompany you on any visits or go in your place to collect your MDR TB drugs?

Yes [ ] No [ ] **If No, go to question 51**

46. On how many visits has your family/friend/DOT supporter accompanied you or gone in your place

a) For scheduled visits for MDR TB assessment/follow up? [ ][ ] times

b) For unscheduled visits to any health care facility? [ ][ ] times

47. How much does your supporter spend on scheduled visits for MDR TB assessment/follow up on:

a) Transport:…… **b)** Food:……

c) Accommodation:…… **d)** Total Costs:……

48. How much does your supporter spend on unscheduled visits to any health care facility on:

a) Transport:…… **b)** Food:……

c) Accommodation:…… **d)** Total Costs:……

49. **a)** Does your friend/family/DOT supporter have an income? Yes [ ] No [ ]

b) If yes, how much per day?……

50. **a)** Why did someone accompany you?

Administrative barriers…… [ ] Distance [ ] Security [ ] Too ill to travel alone [ ]

Was required for treatment [ ] Other [ ]

b) If Other, specify why:……

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

HOSPITALISATION SECTION

51. **a)** Is this the first post-enrolment interview? Yes [ ] No [ ] **If No, go to question 52**

b) Were you hospitalized at post-enrolment period? Yes [ ] No [ ] **If Yes, go to question 53**
If No, go to question 55

52. **a)** Since the previous interview have you been hospitalised again for your MDR TB Treatment?
Yes [ ] No [ ] **If No, go to question 55**

b) How many days in total did you stay at the hospital? [ ][ ][ ] Days

c) How much did you pay in the hospital during your entire stay? (If nothing was spent, enter 0)

i) Total Cost:…… **ii)** Hospital Administration Fees Cost:……

iii) Sheets/Linen Cost:…… **iv)** Food Cost:……

v) Transport Cost: …… **vi)** Drugs: Cost:……

vii) Other Cost:……

d) If Other Cost, specify what:……

53. **a)** Did any family/friend stay with you while in hospital? Yes [ ] No [ ] **If No, go to question 54**

b) How many days in total did family/friend stay with you (sleep there)? [ ][ ][ ] Days

c) How much did your relative/friend pay for staying in the hospital? (enter 0 If nothing spent)

i) Total Cost: …… **ii)** Accommodation Cost: ……

iii) Food: Cost:…… **iv)** Transport Cost:……

v) Other Cost: ……

d) If Other Cost, specify what: ……

e) Does your friend/family/DOT supporter have an income? Yes [ ] No [ ]

f) If Yes, how much per day?……

54. **a)** Did any other family/friend visit you while you were in hospital?
Yes [ ] No [ ] **If No, go to question 55**

b) If Yes, how many people visited you? [ ][ ][ ] Persons

c) How many times did they visit you? [ ][ ][ ] Times

d) What were the costs for your relative/friend who stayed with you in the hospital most recently? (If nothing was spent, enter ***0***)

i) Total Cost: …… **ii)** Accommodation Cost: ……

iii) Food: Cost:…… **iv)** Transport: Cost: ……

v) Other Cost: ……

e) If Other Cost, specify what:……

f) How long were the visits including travelling time? ……hours……minutes

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

OTHER COSTS (since previous interview) SECTION

Food Supplements

55. **a)** Do you (or others – e.g. family members) buy any supplements for your diet because of the MDR TB illness, for example vitamins, meat, energy drinks, soft drinks, fruits or medicines?

Yes [ ] No [ ]

b) If Yes, what kind of items?

i) Fruits:……Yes [ ] No [ ] **ii)** Drinks:……Yes [ ] No [ ] **iii)** Vitamins/herbs:… Yes [ ] No [ ]

iv) Meat: … Yes [ ] No [ ] **v)** Other: ……Yes [ ] No [ ]

c) If Other, specify:……

d) How much did you spend on these items approximately?……

Illnesses

56. **a)** Do you have any chronic illnesses for which you are receiving treatment?

Yes [ ] No [ ] **<u>If No, go to question 57</u>**

b) What is/are the illness (es)?……

c) Are there any additional costs for your household because of this other illness besides the costs that you have already mentioned? Yes [ ] No [ ]

d) If Yes, what were the costs? (If nothing was spent, enter 0)

i) Total Cost: …… **ii)** Tests Cost:……

iii) Drugs Cost:…… **iv)** Transport Cost:……

v) Food Cost:…… **vi)** Other Cost: ……

e) If Other Cost, specify what:……

57. **a)** How much was spent on your healthcare (by you, your household or other family member) on average per month BEFORE the MDR TB illness?……

b) How much is spent on your healthcare (by you, your household or other family member) on average per month NOW?……

Insurance

58. **a)** Do you have any kind of private or government health/medical insurance scheme?

Yes [ ] No [ ]

b) If Yes, what insurance scheme?

i) Reimbursement Scheme: Yes [ ] No [ ] **ii)** Monthly medical allowance:…… Yes [ ] No [ ]

iii) Family/community fund: Yes [ ] No [ ] **iv)** Western Scheme (contract): …… Yes [ ] No [ ]

v) Other:…… Yes [ ] No [ ]

c) If Other, specify:……

STREAM 2
Patient Treatment and Follow Up Costs

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

OTHER COSTS SECTION continued...

Coping Costs

59. **a)** Did you borrow any money to cover costs due to the MDR TB illness since the last interview?
Yes [ ] No [ ] **If No, go to question 60**

b) If Yes, how much did you borrow?..... **c)** When? [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

d) From whom did you borrow?

i) Family: ..... Yes [ ] No [ ]
ii) Neighbours/friends:.....Yes [ ] No [ ]
iii) Private Bank: ..... Yes [ ] No [ ]
iv) Cooperative:..... Yes [ ] No [ ]
v) Other: .....Yes [ ] No [ ]

e) If Other, specify:.....

f) What is the duration of the loan?.....Weeks .....Months ..... Years (single answer)

g) Please indicate the intervals at which repayments are to be made:

Weekly: [ ] Monthly: [ ] Annually: [ ] I am not expected to pay the money back: [ ]
Other: [ ]

h) If Other, specify:.....

i) What is the interest rate on the loan? (%)

Less than 10: [ ] 10 to 15: [ ] More than 15: [ ] I don't pay interest: [ ]

60. **a)** Have you sold any of your property to finance the cost of the MDR TB illness? Yes [ ] No [ ]

b) If Yes, what did you sell?

i) Land: ..... Yes [ ] No [ ]
ii) Livestock: ..... Yes [ ] No [ ]
iii) Transport/vehicle: Yes [ ] No [ ]
iv) Household item: Yes [ ] No [ ]
v) Farm Produce: ..... Yes [ ] No [ ]
vi) Other: ..... Yes [ ] No [ ]

c) If Other, specify:.....

d) What is the estimated market value of the property you sold?:.....

e) How much did you earn from the sale of your property?:.....

Signature:	Printed Name:	Date CRF Completed: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)
Signature:	Printed Name:	Date CRF Verified: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

Date of first database entry: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

Initials of data entry officer: [ ][ ][ ]

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: D D M M M Y Y Y Y — 2 0 2

Patient's Initials:

Study Number: X

PATIENT CONSENT SECTION

The questions on this form are about the patient's social and economic situation and are part of the assessment of patient costs of treatment and the impact of MDR-TB on their life.

Is the patient still willing to provide information on their socioeconomic status? Yes ☐ No ☐

If 'No', please do not continue with the rest of this form.

INDIVIDUAL SITUATION AND INCOME SECTION

Primary Earner

1. **a)** Who is usually the primary income earner in the household? ***(tick one box only)***

Wife/mother/partner……. ☐ Husband/Father/Partner ☐ Patient…… ☐

Son/daughter …… ☐ Extended family ☐ Other…… ☐

b) If Other, specify:……

Education

2. **a)** What is the highest level of education of the patient?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other…… ☐

b) If Other, specify:……

3. **a)** What is the highest level of education of the primary income earner?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other …… ☐

b) If Other, specify:……

4. **a)** What is the highest level of education of the Head of the Household?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know…… ☐ Other …… ☐

b) If Other, specify:……

5. **a)** What is the highest level of education of the Spouse of the Head of the Household?

Not attended/illiterate ☐ Primary…… ☐ Secondary… ☐

Graduate/certificate…… ☐ Don't know …… ☐ Other …… ☐

N/A…… ☐

b) If Other, specify:……

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

INDIVIDUAL SITUATION AND INCOME SECTION continued...

Employment and family

6. **a)** Are you currently formally employed?

Yes, formal work [ ]	(go to 13)	No, informal work [ ]	(go to 13)
On sick leave [ ]	(go to 7)	Retired [ ]	(go to 11)
School, university [ ]	(go to 16)	Housework [ ]	(go to 13)
No, not working [ ]	(go to 7)	Other [ ]	(go to 6b)

b) If Other, specify:.....

7. **a)** Is the reason for not working related to the illness that led to your enrolment in the trial?

Yes [ ] No [ ]

b) If Yes, when was the last time you were working? [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

8. Did you become financially dependent on somebody because of illness? Yes [ ] No [ ]

9. **a)** Have you ever stopped working/going to school/doing housework due to the illness that led to enrolment in the trial?

Yes [ ] No [ ]

b) If Yes, for how long?

Less than 1 month [ ] One month [ ] 2-3 months [ ] 4-5 months [ ]

More than 6 months [ ]

10. **a)** Does someone stay home specifically to take care of you because of your illness? Yes [ ] No [ ]

b) If Yes, for how long? [ ][ ] Weeks

c) If Yes, did they quit their income-earning job to stay home and care for you?.....Yes [ ] No [ ]

11. **a)** How regularly did you work before you became ill with the illness that led to enrolment in the trial?

Throughout the year [ ] Seasonal/part of the year [ ] Day labour [ ] Other [ ]

b) If Other, specify:.....

12. Did you have to change jobs when you became ill with the illness that led to enrolment in the trial?

Yes [ ] No [ ]

13. **a)** What is your main occupation?

Sales/service... [ ] Agriculture... [ ] Household duties... [ ] Production/construction... [ ]

Other..... [ ]

b) If Other, specify:.....

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

INDIVIDUAL SITUATION AND INCOME SECTION continued…

14. **a)** How are you usually paid?

Cash [ ] In kind [ ] Not paid [ ] Bank transferred salary [ ] Other [ ]

b) If Other, Specify:……

15. **a)** How are you usually paid? Per day [ ] Per month [ ] Don't earn [ ]

b) What was your estimated personal take home earning BEFORE the illness that led to enrolment in the trial? (includes welfare, disability, or other social support)……

c) Are you a housewife? Yes [ ] No [ ] **<u>If Yes, go to question 16</u>**

d) What is your estimated personal take home earning NOW? (includes welfare, disability, or other social support) ……

e) Don't earn? Yes [ ] No [ ]

f) *If answer to 15d differs from 15b,* is the change related to the illness that led to enrolment in the trial? Yes [ ] No [ ]

16. **a)** How many hours did you work/study on average per day BEFORE you became ill with the illness that led to enrolment in the trial? Hours [ ][ ]

b) How many hours do you work/study on average NOW per day? [ ][ ] Hours

c) *If answer to 16a differs from 16b,* is the change related to the illness that led to enrolment in the trial?

Yes [ ] No [ ]

d) *If answer to 16a differs from 16b,* is someone doing the work that you used to do?

Yes [ ] No [ ]

e) If Yes: **i)** Daughter ..Yes [ ] No [ ] **ii)** Son……..Yes [ ] No [ ] **iii)** Spouse… Yes [ ] No [ ]

iv) Friend……Yes [ ] No [ ] **v)** Other Family...Yes [ ] No [ ]

17. **a)** Do you have children of or below school age? Yes [ ] No [ ] **<u>If No, go to question 18</u>**

b) Do all of your children of school age attend school regularly? Yes [ ] No [ ]

c) If No, why not?

i) Needs to help around the house. Yes [ ] No [ ] **ii)** No money for school fees…Yes [ ] No [ ]

iii) Has to work to earn income…..Yes [ ] No [ ] **iv)** Also sick……Yes [ ] No [ ]

v) Other……...Yes [ ] No [ ]

d) If Other, specify:……

e) Do any of your children of or below school age work to finance costs due to the illness that led to enrolment in the trial:

Yes [ ] No [ ]

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

INDIVIDUAL SITUATION AND INCOME SECTION continued...

18. Imagine if you employed someone to do the housework for your household, how much would you have to pay him/her per month? **Ai)** While you are sick …… **Aii)** Don't know [ ]

Bi) While you are healthy:…… **Bii**) Don't know [ ]

19. **a)** Has the illness that led to your enrolment affected your social or private life in any way?

Yes [ ] No [ ] **<u>If No, go to question 20</u>**

b) If Yes, how?

i) Loss of job…Yes [ ] No [ ] **ii)** Dropped out of school…… …..Yes [ ] No [ ]

iii) Divorce…… Yes [ ] No [ ] **iv)** Separated from spouse/partner ……..Yes [ ] No [ ]

v) Sick child… Yes [ ] No [ ] **vi)** Disruption of sexual life…….... Yes [ ] No [ ]

vii) Other……Yes [ ] No [ ]

c) If Other, specify:……

d) Has this resulted in a financial burden? Yes [ ] No [ ]

20. How much was spent on your healthcare (by you, your household or other family member) on average per month BEFORE the illness that led to enrolment in the trial:……

21. **a)** What is your ethnicity?……

b) What is your religion? ……

HOUSEHOLD STRUCTURE AND COSTS SECTION

Residents

22. How many people regularly sleep in your house? (including patient): [ ][ ] persons

23. How many of the household members are paid for working? (including patient) (includes payment in kind or farm produce): [ ][ ] persons

24. **a)** Besides yourself, does anyone else of your household receive treatment for MDR TB?

Yes [ ] No [ ] *If patient lives alone, answer 'No' and from Q25 onwards replace the word 'household' with 'you'*

b) If Yes, how many? [ ][ ] persons

Food Consumption

25. What is the proportion of the total food consumed every month that:

a) Was purchased? ……

b) Was produced at home?……

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

HOUSEHOLD STRUCTURE AND COSTS SECTION continued...

26. **a)** How much food did your household purchase every month on average BEFORE the illness that led to enrolment in the trial? Total Cost:……

b) If the food that you produced at home per month BEFORE the illness that led to enrolment in the trial was sold on the market, how much would it be worth? Total Cost:……

c) How much food does your household purchase NOW every month on average? Total Cost:……

d) If the food that you produce at home per month NOW was sold on the market, how much would it be worth? Total Cost:……

e) If answer to 26a differs from 26c, has the amount of food consumed per month changed due to the illness that led to enrolment in the trial? Yes ☐ No ☐

SOCIOECONOMIC INDICATORS SECTION

27. What is your electricity supply?
Own Connection ☐ Shared Connection ☐ None ☐

28. What is your source of drinking water? (Choose one answer)
Lake/pond/dam/river ☐ Protected well… ☐ Bore hole …… ☐ Unprotected spring ☐
Piped into dwelling…… ☐ Piped into yard ☐ Public tap/standpipe ☐

29. How many rooms are there in your house?
1 Room ☐ 2 Rooms ☐ 3 Rooms ☐ 4 Rooms ☐ More than 4 ☐

30. **a)** Current place of residence? (*in Amharic version Urban slum is deleted)*
Urban ☐ Urban Slum ☐ Rural ☐ Other ☐

b) If Other, specify:……

31. Do you own the house of residence you live in? Yes ☐ No ☐

32. **a)** What power do you use for cooking most frequently? (Choose one answer)
Own electricity connection …… ☐ Shared electricity connection ☐ Gas… ☐ Paraffin ☐
Charcoal or purchased firewood ☐ Collected firewood …… ☐ Other ☐

b) If Other, specify:……

STREAM 2

Patient Socioeconomic Status: Baseline

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

SOCIOECONOMIC INDICATORS SECTION continued...

33. **a)** Where is your place for cooking? (Choose one answer)

In the house [ ] In a separate building [ ] Outdoors [ ] No food is cooked in the house [ ]

Other..... [ ]

b) If Other, specify:.....

34. **a)** What is the floor in your house made from? (Choose one answer)

Earth/sand [ ] Dung [ ] vinyl/asphalt [ ] Cement [ ] Other [ ]

b) If Other, specify:.....

35. **a)** Do you own:

i) Radio ..... Yes [ ] No [ ]
ii) Mobile phone..... Yes [ ] No [ ]
iii) Television..... Yes [ ] No [ ]
iv) Non-mobile phone ..... Yes [ ] No [ ]
v) Refrigerator..... Yes [ ] No [ ]
vi) Bicycle ..... Yes [ ] No [ ]
vii) Animal-drawn cart.....Yes [ ] No [ ]
viii) Motorcycle/Scooter.....Yes [ ] No [ ]
ix) Car/truck.....Yes [ ] No [ ]
x) Livestock (farm animals).....Yes [ ] No [ ]
xi) Land..... Yes [ ] No [ ]

b) If you own land, quantify:.....

36. **a)** If the government could provide you with some service to ease the burden of the illness that led to enrolment in the trial on you and your household, what would you prefer to have?

i) Transport Vouchers..... Yes [ ] No [ ]
ii) Food vouchers..... Yes [ ] No [ ]
iii) More efficient service... Yes [ ] No [ ]
iv) Housing support.....Yes [ ] No [ ]
v) Other..... Yes [ ] No [ ]

b) If Other, please explain some more:.....

Thank you for your cooperation! Is there anything you would like to ask or say?

Signature:	Printed Name:	Date CRF Completed: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)
Signature:	Printed Name:	Date CRF Verified: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

Date of first database entry: [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

Initials of data entry officer: [ ][ ][ ]

STREAM 2

Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

PATIENT CONSENT SECTION

The questions on this form are about the patient's social and economic situation and are part of the assessment of patient costs of treatment and the impact of MDR-TB on their life.

Is the patient still willing to provide information on their socioeconomic status? Yes [ ] No [ ]

If 'No', please do not continue with the rest of this form.

INDIVIDUAL SITUATION AND INCOME SECTION

Employment and family

1. **a)** Are you currently formally employed? (***tick one box only***)

Yes, formal work [ ] (go to 5) No, informal work [ ] (go to 5) On sick leave [ ] (go to 2)
Retired [ ] (go to 2) School, university [ ] (go to 8) Housework [ ] (go to 3)
No, not working [ ] (go to 2) Other [ ] (go to 1b)

b) If Other, specify:……

2. **a)** Is the reason for not working related to the illness that led to your enrolment in the trial?

Yes [ ] No [ ]

b) If Yes, when was the last time you were working? [ ][ ] [ ][ ][ ] [2][0][ ][ ] (D D M M M Y Y Y Y)

3. Are you financially dependent on somebody because of illness?…… Yes [ ] No [ ]

4. **a)** Does someone stay home specifically to take care of you?…… Yes [ ] No [ ]

b) If yes, for how long? [ ][ ] Weeks

c) Did they quit their income-earning job to stay home and care for you?… Yes [ ] No [ ]

5. **a)** What is your main occupation?:

Sales/service [ ] Agriculture [ ] Household [ ] Production/construction [ ] Other [ ]

b) If Other, specify:……

6. **a)** How are you usually paid?

Cash [ ] In kind [ ] Not paid [ ] Bank transferred salary [ ] Other [ ]

b) If Other, specify:……

7. **a)** How are you usually paid? Per day [ ] Per month [ ] Don't earn [ ]

b) What is your estimated personal take home earning NOW (includes welfare, disability, or other social support):……

c) Are you a housewife? Yes [ ] No [ ]

STREAM 2

Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

INDIVIDUAL SITUATION AND INCOME SECTION continued...

8. How many hours do you work/study on average NOW per day? [ ][ ] Hours

9. **a)** Do you have children of or below school age? Yes [ ] No [ ] **If No, go to question 10**

b) Do all of your children of school age attend school regularly? Yes [ ] No [ ]

c) If No, why not?

i) Needs to help around the house: Yes [ ] No [ ] **ii)** No money for school fees:.....Yes [ ] No [ ]

iii) Has to work to earn income:..... Yes [ ] No [ ] **Iv)** Also sick:.....Yes [ ] No [ ]

v) Other: ..... Yes [ ] No [ ]

d) If Other, specify:.....

e) Do any of your children of or below school age work to finance costs due to the illness that led to enrolment in the trial: Yes [ ] No [ ]

10. Imagine if you employed someone to do the housework for your household, how much would you have to pay him/her per month? **Ai)** While you are sick: ..... **Aii)** Don't know [ ]

Bi) While you are healthy:..... **Bii)** Don't know [ ]

11. **a)** Has the illness that led to your enrolment affected your social or private life in any way?

Yes [ ] No [ ] **If No, go to question 12**

b) If Yes, how?

i) Loss of job:..... Yes [ ] No [ ] **ii)** Dropped out of school:..... Yes [ ] No [ ]

iii) Divorce:.....Yes [ ] No [ ] **iv)** Separated from spouse/partner:... Yes [ ] No [ ]

v) Sick child:..... Yes [ ] No [ ] **vi)** Disruption of sexual life:..... Yes [ ] No [ ]

vii) Other..... Yes [ ] No [ ]

c) If Other, specify:.....

d) Has this resulted in a financial burden?.....Yes [ ] No [ ]

12. **a)** Do you receive any of these services to ease the burden of the illness that led to enrolment in the trial?

i) Transport Vouchers:..... Yes [ ] No [ ] **ii)** Food vouchers:.....Yes [ ] No [ ]

iii) Housing support :.....Yes [ ] No [ ] **iv)** Other :.....Yes [ ] No [ ]

b) If Other, specify:.....

STREAM 2

Patient Socio-economic Status: Generic

Visit Date: [ ][ ] [ ][ ][ ] [2][0][2][ ] (D D M M M Y Y Y Y)

Patient's Initials: [ ][ ][ ]

Study Number: [ ][ ][ ][ ][ ][ ][X]

Week Number: [ ][ ][ ]

HOUSEHOLD STRUCTURE AND COSTS SECTION

Residents

13. How many people regularly sleep in your house? (including patient) [ ][ ] persons

If patient lives alone, go to question 16 and replace the word 'household' with 'you'.

14. How many of the household members are paid for working? (including patient)

(includes payment in kind or farm produce):…… [ ][ ] persons

15. **a)** Besides yourself, does anyone else of your household receive treatment for MDR TB?

Yes [ ] No [ ]

b) If yes, how many people? …… [ ][ ] persons

Food Consumption

16. What is the proportion of the total food every month that:

ai) Was purchased? …… **aii)** Was produced at home?……

b) How much food does your household purchase NOW every month, on average?

Total Cost:……

c) If the food that you produced at home per month NOW was sold on the market, how much would it be worth? Total Cost:……

SOCIOECONOMIC INDICATORS SECTION

17. What is your electricity supply?

Own Connection [ ] Shared Connection [ ] None [ ]

18. What is your source of drinking water? (Choose one answer)

Lake/pond/dam/river [ ] Protected well… [ ] Bore hole ……..… [ ] Unprotected spring [ ]

Piped into dwelling…… [ ] Piped into yard [ ] Public tap/standpipe [ ]

19. How many rooms are there in your house?

1 Room…… [ ] 2 Rooms [ ] 3 Rooms [ ] 4 Rooms [ ] More than 4 [ ]

20. **a)** Current place of residence? (Urban slum is deleted in Amharic version)

Urban…… [ ] Urban Slum [ ] Rural [ ] Other [ ]

b) If Other, specify:……

c) Do you own the house or residence you live in? Yes [ ] No [ ]

STREAM 2

Patient Socio-economic Status: Generic

Visit Date: ☐☐ ☐☐☐ 2 0 2 ☐ (D D M M M Y Y Y Y)

Patient's Initials: ☐☐☐

Study Number: ☐☐☐☐☐☐X

Week Number: ☐☐☐

SOCIOECONOMIC INDICATORS SECTION continued...

21. **a)** What power do you use for cooking most frequently? (Choose one answer)

Own electricity connection …… ☐ Shared electricity connection ☐ Gas… ☐ Paraffin ☐

Charcoal or purchased firewood ☐ Collected firewood…… ☐ Other ☐

b) If 'Other', please specify:……

c) Where is your place for cooking? (Choose one answer)

In the house ☐ In a separate building ☐ Outdoors ☐ No food is cooked in the house ☐

Other…… ☐

d) If Other, specify:……

22. **a)** What is the floor in your house made from? (Choose one answer)

Earth/sand ☐ Dung ☐ Vinyl/asphalt ☐ Cement ☐ Other ☐

b) If Other, specify:……

23. **a)** Do you own:

i) Radio…… Yes ☐ No ☐ **ii)** Mobile phone…… Yes ☐ No ☐

iii) Television…… Yes ☐ No ☐ **iv)** Non-mobile phone…… Yes ☐ No ☐

v) Refrigerator…… Yes ☐ No ☐ **vi)** Bicycle…… Yes ☐ No ☐

vii) Animal-drawn cart…… Yes ☐ No ☐ **viii)** Motorcycle/Scooter …… Yes ☐ No ☐

ix) Car/truck…… Yes ☐ No ☐ **x)** Livestock (farm animals) Yes ☐ No ☐

xi) Land:…… Yes ☐ No ☐

b) If you own land, please quantify:……

Signature:	Printed Name:	Date CRF Completed: ☐☐ ☐☐☐ 2 0 ☐☐ (D D M M M Y Y Y Y)
Signature:	Printed Name:	Date CRF Verified: ☐☐ ☐☐☐ 2 0 ☐☐ (D D M M M Y Y Y Y)

Date of first database entry: ☐☐ ☐☐☐ 2 0 ☐☐ (D D M M M Y Y Y Y)

Initials of data entry officer: ☐☐☐