Addressing the challenges of recurrent tuberculosis in Malawi

Thesis submitted in accordance with the requirements
of the University of Liverpool for the
degree of Doctor in Philosophy by

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TB Retreatment Regimen
Outcomes & Care Study

Declaration

This thesis is the result of my own work. In some instances, the work was done in conjunction with other colleagues and institutions. The table below details the contributions made by others to this work.

This research was carried out at The Malawi-Liverpool-Wellcome Research Programme, Blantyre, Malawi.

The material contained in this thesis has not been presented, nor is it currently being presented, either wholly or in part, for any other degree or qualification.

Responsibilities for work carried out as part of the TB-RROC Study

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MLW	*Malawi Liverpool Wellcome Clinical Research Programme*
LSTM	*Liverpool School of Tropical Medicine*
CoM	*Malawi College of Medicine*
MoH	*Malawi Ministry of Health*
QECH	*Queen Elizabeth Central Hospital*
NTP	*Malawi National TB Control*
UoW	*University of Warwick*
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Abstract

Background

Each year, approximately 10% of people diagnosed with tuberculosis (TB) globally have previously received TB treatment, and are prescribed a standardised WHO 'Category II regimen' which includes daily intramuscular injections of streptomycin. Treatment success rates on this re-treatment regimen are low, yet reasons for poor outcomes are not well understood. Currently data are lacking about appropriate ways to deliver long term injectable agents used as part of TB treatment.

Methods

The study was conducted in Malawi, a small country in South-Eastern Africa with a high TB burden and a generalised HIV epidemic. A cohort study prospectively recruited adult patients receiving retreatment regimen. Patients were assessed at baseline, 2 and 8 months. Multivariate logistic regression analysis was used to determine associations between clinical outcome and microbiologically confirmed TB, drug resistance, clinical features at presentation and medical co-morbidities. A pragmatic, individually randomised trial assessed hospital versus community-based care during the intensive phase of TB retreatment. In the community arm guardians were trained to deliver intramuscular injections of streptomycin at home. An economic evaluation was conducted from a societal perspective; and a qualitative evaluation involved in depth interviews with trial participants, key informant interviews, and observations.

Results

In the cohort study, the prevalence of drug resistance was 9.6%. The prevalence of co-morbidity was high (HIV 82.9%; antiretroviral therapy failure 37.5%; severe anaemia 22.2%; chronic lung disease 88.2%; renal impairment 33.8%). Ototoxicity developed in 35.9% and nephrotoxicity in 14.6%. In multivariate analysis, successful outcome was associated only with hypotension at presentation, but not microbiologically confirmed TB, drug resistance or other co-morbidities. In the trial, 93.2% of patients who received community-based care successfully completed 2 months treatment, compared to 96.0% managed in hospital (RD -0.03; 95%CI -0.09 - 0.03). The mean cost of hospital-based care was US$ 1546 per person, compared to US$ 729.2 in the community. Community-based management reduced risk of catastrophic household costs by 84%. Qualitative data demonstrated social and financial benefits of community-based care.

Conclusions

This cohort study demonstrated a low prevalence of drug resistant TB but a high burden of medical co-morbidity in patients with recurrent TB in Malawi. Co-morbidity is likely to be contributing to poor outcomes on TB retreatment regimen. A novel community-based model of delivering injectable anti-TB drugs by training guardians to do injections at home is shown to be feasible, acceptable and highly cost effective.

Abbreviations

AAFB	Acid Alcohol Fast Bacilli
ADR	Adverse Drug Reaction
ALT	Alanine transaminase
ART	Anti Retroviral Therapy
CAB	Community Advisory Board
CADR	Cutaneous Adverse Drug Reaction
CALFRAST	Calibrated finger rub auditory screening test
CAO	Chronic Airways Obstruction
COM	Malawi College of Medicine
COPD	Chronic Obstructive Pulmonary Disease
CPA	Chronic Pulmonary Aspergillosis
CrCl	Creatinine Clearance
CRF	Case Record Form
CT	Computerised Tomography
DILI	Drug Induced Liver Injury
DM	Diabetes Mellitus
DOT	Directly observed therapy
DSMB	Data and Safely Monitoring Board
DST	Drug Sensitivity Testing
ENT	Ear, Nose & Throat
EPTB	Extrapulmonary Tuberculosis
FBC	Full Blood Count
FGD	Focus Group Discussion
GCP	Good Clinical Practice
GXP	Xpert ®MTB/RIF assay
HbA1c	Glycosolated Haemoglobin
HCAI	Health care associated infection
HIV	Human Immunodeficiency Virus
HSA	Health Surveillance Assistant
HTC	HIV testing and counselling
IDI	In-depth interview
IFNγ	Interferon-γ
IRIS	Immune Reconstitution Inflammatory Syndrome
KI	Key Informant
LJ	Lowenstein Jensen
MDR-TB	Multidrug Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MLW	Malawi Liverpool Wellcome Clinical Research Programme
MOH	Malawi Ministry of Health

MOTT	Mycobacteria Other Than Tuberculosis
MRC	Medical research council
NGO	Non-governmental organisation
NIHR	National Institute for Health Research
NTP	National Tuberculosis Control Program
ODI	The Overseas Development Institute
OPAT	Outpatient parenteral antibiotic therapy
PBS	Phosphate Buffered Saline
PI	Principal Investigator
PTA	Pure Tone Audiometry
PTB	Pulmonary Tuberculosis
QECH	Queen Elizabeth Central Hospital
RA	Research Assistant
RAPID	Research and policy in Development
RCT	Randomised Controlled Trial
RIFLE	Risk, Injury, Failure, Loss of function, ESRD
TAD	Treatment after default
TB	Tuberculosis
TCA	Thematic content analysis
TDL	Tuberculous Destroyed Lung
TEOAEs	Transiently Evoked Otoacoustic Emissions
The Union	The International Union Against Tuberculosis and Lung Disease
TSC	Trial Steering Committee
TTP	Time to positivity
WHO	World Health Organisation
WTTC	Wellcome Trust Tropical Centre
XDR-TB	Extensively Drug Resistant Tuberculosis
ZN	Ziehl Neelsen

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1 Introduction and literature review

1.1 Introduction

1.1.1.1

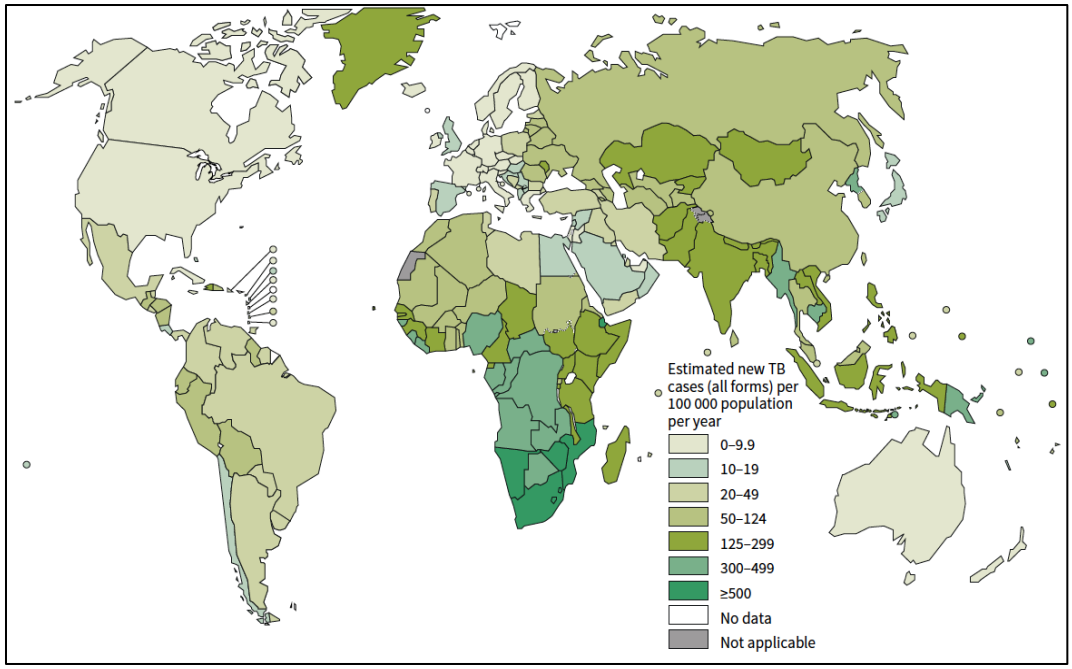
Of the 6.1 million people worldwide reported to have tuberculosis (TB) in 2013, 600,000 were registered as having previously received TB treatment. These patients receive a regimen which has little evidence base, have consistently poor treatment outcomes, and are required to have daily intramuscular injections of streptomycin for the first 2 months of treatment. It is for these reasons that recurrent TB places a disproportionate burden on patients, households and health systems. Although the rates of successful completion of TB retreatment are low, no prospective study has systematically attempted to address why this is so. Additionally, there is a lack of evidence for appropriate approaches to the delivery of injectable agents as a part of TB treatment. This thesis therefore addresses two key issues for patients with recurrent tuberculosis: why so many fail to complete treatment, and how injectable agents can best be delivered using a novel approach to community-based care.

This introductory chapter reviews the current literature on issues relevant to the management of recurrent tuberculosis (TB). It begins by providing a general summary of key concepts in the epidemiology, clinical features and control of tuberculosis both globally and in Malawi, before going on to focus on retreatment TB in more detail. A systematic review of the literature on clinical outcomes in treatment for recurrent TB is then presented, following which reasons for poor outcomes on treatment are explored, such as co-morbidity and toxicity of anti-tuberculous drugs. Finally, evidence is examined for community and hospital-based approaches to the delivery of injectable anti-tuberculosis drugs.

1.2 Tuberculosis

Tuberculosis (TB) has plagued humankind since ancient times [1], and is likely to have been responsible for killing more people than any other pathogen [2]. Since the tubercle bacillus was discovered by Robert Koch in 1882 [3], there have been great advances in diagnosis and management of the disease. Yet it remains a global public health problem, causing nearly 9 million cases and 1.5 million deaths annually [4], predominantly in low and middle income countries (figure 1). Tuberculosis still disproportionately affects the poorest and most vulnerable members of society - it therefore has implications beyond clinical disease and cannot be viewed in isolation from the social and financial burdens with which it is frequently associated [5].

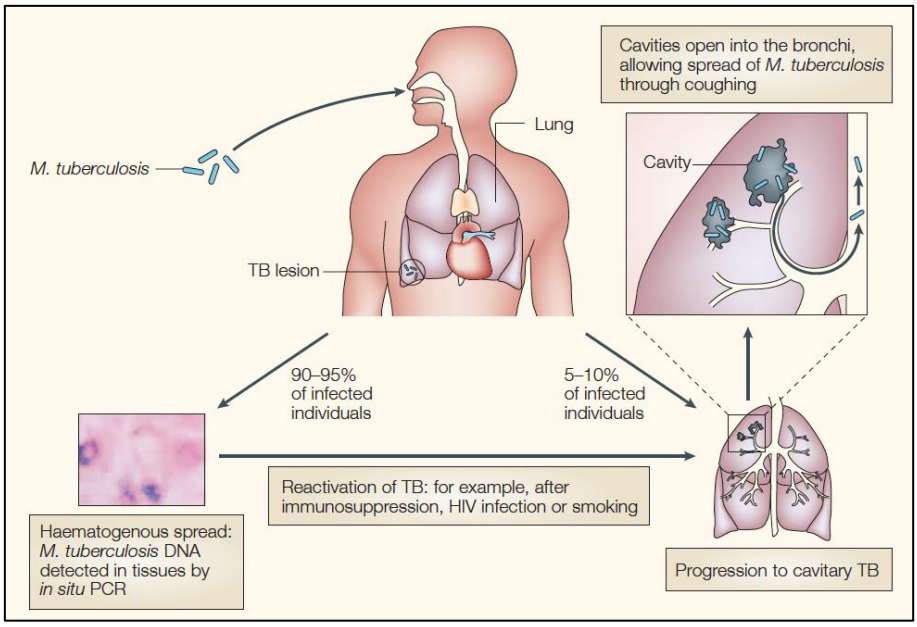
Figure 1. Global incidence of tuberculosis. Global tuberculosis report, 2014 [4].



1.2.1 Microbiology and pathogenesis of tuberculosis

The bacterium *Mycobacterium tuberculosis* is a member of a group of organisms known as the *M. tuberculosis* complex, which also includes its close relatives *M. africanum* and *M. bovis* [6]. It is transmitted between human hosts by inhalation of aerosolised droplets, and once in the lungs predominantly infects alveolar macrophages [7]. Following a brief phase of haematogenous spread, a series of immunological responses then result in the formation of the characteristic tuberculous granuloma whose primary function is to contain replication and prevent dissemination of mycobacteria beyond the lungs [8]. In a minority of people, symptomatic active disease, usually limited to the thoracic cavity, develops at this stage. However, in approximately 90% of infected individuals infection remains latent, often for many decades [9]. Disease can reactivate at any time, usually in response to immunosuppression by factors such as HIV, immunosuppressive drugs, diabetes, alcoholism, malnutrition or stress [10]. During active pulmonary disease, granulomas within the lung parenchyma caseate and eventually rupture, releasing thousands of infectious bacilli into the airways. This causes the infected individual to cough, aerosolising and therefore facilitating further transmission of mycobacteria [11].

Figure 2. The pathogenesis of M. tuberculosis. From Rook et al [10]



1.2.2 Clinical features, presentation and management of tuberculosis

The clinical features of tuberculosis relate to the site of active disease and are frequently accompanied by constitutional symptoms such as fever, night sweats and weight loss. Pulmonary tuberculosis classically presents with chronic cough, sputum production and haemoptysis. Extra-pulmonary disease occurs in 10 to 42% of patients [12], and can affect almost any organ including pleura, central nervous system, pericardium, skeleton, lymph nodes, bone marrow, genito-urinary tract, gastrointestinal tract and skin [13]. People who are HIV infected are not only at increased risk of developing TB, they also present less frequently with classic features of pulmonary tuberculosis, and are more likely to have disseminated disease (section 1.6.1).

The lack of a good diagnostic tool for tuberculosis has been one of the major challenges in TB control. For many years, the diagnosis of tuberculosis depended entirely on the demonstration of bacilli in the sputum using the staining technique developed by Ziehl and Neelsen in the 1890s [14]. Although relatively inexpensive and technically uncomplicated, sputum smear microscopy lacks sensitivity, despite advances such as the introduction of LED microscopy [15, 16]. Culture of mycobacteria on solid media was developed in the 1930s by Lowenstein and Jensen which improved sensitivity, but its application is still hampered by long incubation times. Since then, liquid culture techniques have significantly reduced time to detection and increased sensitivity further, and are now replacing solid culture as the gold standard of TB diagnosis [17]. More recently, ground-breaking discoveries in the use of molecular techniques have brought about the Xpert ®MTB/RIF (GXP) and Line Probe Assays which offer not only the opportunity of rapid diagnosis but also the ability to detect drug resistance in real time [18, 19]. Nevertheless, these tests still pose technical and financial challenges and their impact on patient important outcomes in operational situations is still debated [20].

Streptomycin (S), the first drug for the treatment of tuberculosis, was developed in 1946. By 1948 the first randomised clinical trial was conducted by the British

Medical Research Council in which streptomycin was shown to reduce mortality from tuberculosis [21]. However, it soon became clear that therapy using only a single drug rapidly resulted in the development of drug resistance [22], and ever since that time anti-tuberculous agents have been used in combination. During the following decades, combination 'short course' chemotherapy was developed based on a series of clinical trials which demonstrated that both rifampicin and pyrazinamide were required in the regimen; that rifampicin was sterilizing throughout treatment; and that the minimum period for the intensive phase was two months [23]. The 2010 World Health Organisation Guidelines for the Treatment of Tuberculosis recommend two standardised first-line combination regimens. Firstly, all new patients with pulmonary TB should receive a six month regimen consisting of a two month 'intensive phase' of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E); followed by a four month 'continuation phase' of RH. Secondly, all patients presenting with tuberculosis who have previously received treatment should receive the extended 'Category II' or 'retreatment' regimen, which consists of 2RHZES/1RHZE/5RHE [24].

1.2.3 The recent epidemiology of tuberculosis

Over the past three decades, the emergence of Multidrug-resistant TB (MDR-TB) has posed a major threat to efforts aimed at controlling TB, particularly in Eastern Europe, parts of Sub-Saharan Africa, South America, and Asia [25]. Patients infected with a strain of *M. tuberculosis* which is resistant *in vitro* to both rifampicin and isoniazid require lengthy treatment, which currently consists of one injectable agent and at least four other second-line drugs, most of which have poorer efficacy and greater toxicity than first line agents [26]. Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to any quinolone and any injectable agent, and outcomes for people infected with XDR-TB are extremely poor [27].

In addition to MDR-TB, the global response to TB has had to face the increasing problem of co-infection with HIV, particularly in Sub-Saharan Africa. Whilst it is Asian countries which have the highest number of TB cases globally, the HIV

epidemic in Sub-Saharan Africa has fuelled the highest incidence rate of in the world, where HIV prevalence amongst new TB cases is >50% in many countries (figure 3). The close association between TB and HIV led to a peak in global incidence rates in 2004, which has been gradually declining since then (figure 4).

A major challenge in TB control is to address the issue that tuberculosis has historically been, and still is, strongly associated with poverty. Currently, of the 22 high TB burden countries, 17 are classified as low or lower-middle income [28], and the incidence rate of tuberculosis has been declining more quickly in countries with a higher human development index [29]. Factors which drive the association between low socio-economic status and tuberculosis include increased risk of transmission because of higher rates of contact with infectious cases; over-crowded and poorly ventilated living and working conditions; increased progression from infection to disease driven by factors such as poor nutrition; and reduced access to good health care [5, 30-32]. The link between poverty and tuberculosis is further driven by the costs of diagnosis and care which frequently worsen already fragile economic situations in households affected by tuberculosis [33, 34].

Figure 3. HIV prevalence amongst new TB cases [35]

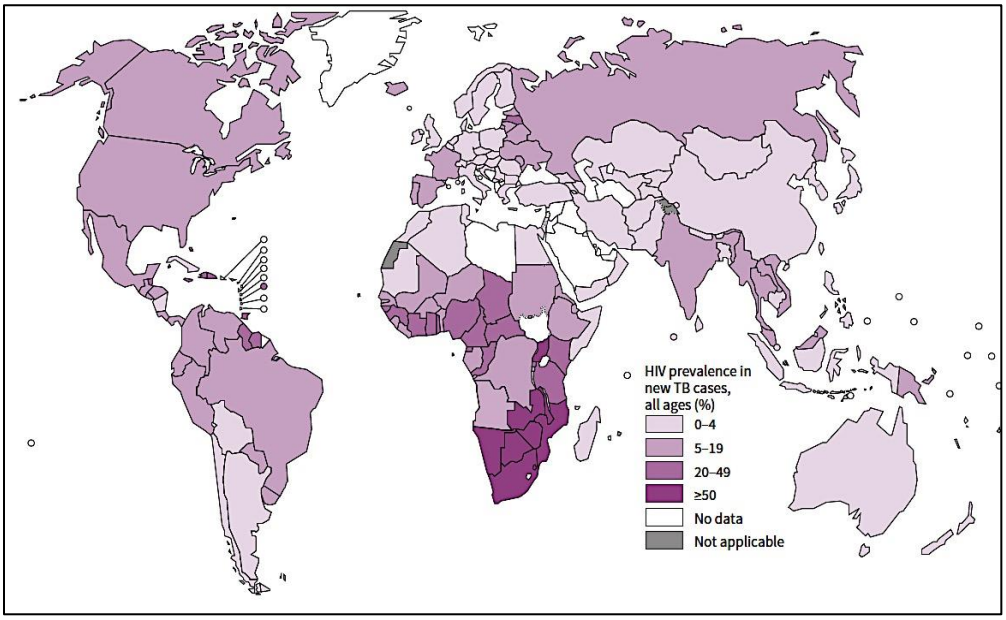
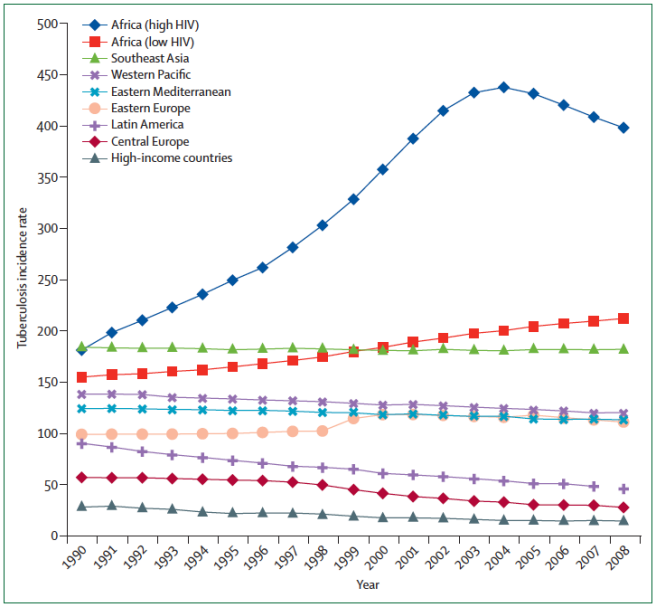


Figure 4. TB incidence according to region. Data from Zumla et al [12]



1.3 Tuberculosis retreatment

Each year, approximately 11% of all people registered for TB treatment have previously received treatment [4]. These patients fall into a number of categories (table 1) [36][1]. In 2013, of the 6.1 million people notified to National TB Control Programmes worldwide, 0.3 million were classified as 'relapse', and a further 0.4 million had either failed, defaulted or been previously treated for another reason.

Table 1. WHO definitions of TB retreatment category

Category	Definition
Relapse	A patient previously treated for TB, declared cured or treatment completed, who is diagnosed again with smear or culture positive TB
Treatment after failure	A patient who is stared on retreatment regimen after having failed previous treatment
Treatment after default	A patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 or more consecutive months
Other previously treated	All previously treated cases that do not fit any of the above definitions. e.g. previously treated smear negative cases, previously treated EPTB

[1] In 2013, new definitions were produced by the WHO, however the 2006 definitions are used in this thesis, as the study protocol was devised prior to publication of the revised guidelines. (http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf).

Recurrence of tuberculosis can be caused by two distinct mechanisms. Firstly, disease can be caused by relapse of the original infecting mycobacterial strain (note the difference between this definition and the operational definition of 'relapse' in table 1). Secondly, patients can be exogenously re-infected with an entirely new strain, unrelated to the one which caused their first episode [37]. Molecular techniques allow differentiation between re-infection and relapse by analysing strains isolated from sputum collected during an initial episode, and comparing them to strains isolated from subsequent episodes [38]. Patterns of relapse and reinfection are strongly associated with HIV status - work from South Africa [39, 40], India [41] and Malawi [42, 43] has consistently demonstrated that HIV infection is associated with re-infection, but not with relapse. Possible explanations for this are that HIV positive patients remain at increased risk of reinfection because of on-going impaired immunity and increased exposure (e.g. from frequent contact with health care facilities).

It has long been clear that recurrence is most common in the first two years following an initial episode [44]. However, once again, genetic analysis of mycobacterial strains has meant that it has been possible to distinguish temporal patterns of relapse and reinfection. For example, large studies in Northern Malawi and Cape Town have recently used genomic sequencing to show that most relapse occurs in the first year, but that recurrence due to reinfection is rare during the first year [45, 46]. It is perhaps unsurprising therefore that relapse is associated with unsuccessful initial treatment and drug resistance [43]; whereas reinfection is more likely to suggest inadequate development of protective immunity and on-going exposure.

Due to the increased risk of drug resistance in this group, it is crucial that all patients being 'retreated' for TB have sputum examined for Drug Sensitivity Testing (DST), using either genotypic or phenotypic methods [24]. However, in many areas of the world, access to DST still poses significant challenges. WHO policy states that previously treated patients who are not diagnosed with MDR-TB should receive the standardised WHO Category II regimen. There is a lack of clinical trial evidence to

suggest efficacy of this regimen, which was developed by expert consultation in the 1990s. Additionally, it puts patients at a potentially increased risk of drug toxicity due to the longer duration and greater number of drugs; and brings with it operational problems of delivering daily injectable agents during the intensive phase. Nevertheless, a Global Consultation on Retreatment Regimens in 2009 did not suggest the discontinuation of Category II treatment [47], and the most recent WHO guidelines in 2010 still recommend the empiric use of routine Category II regimen in settings where the prevalence of MDR-TB is low and DST is not available [24].

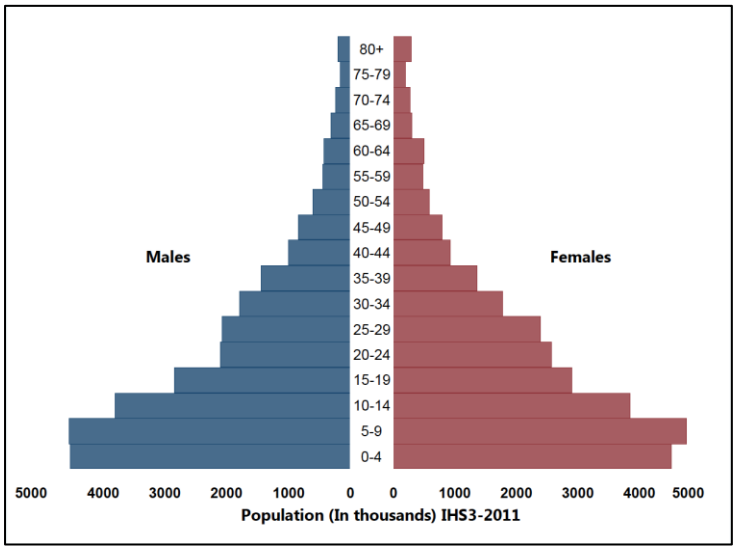
1.4 Tuberculosis in Malawi

1.4.1 Demographic and health indicators in Malawi

Malawi is a land locked country in the south-east of Africa with an area of approximately 120,000 square kilometres. In 2013, the population was estimated at 16,363,000, of whom 84% lived in rural areas [48]. The World Bank recently rated Malawi the poorest country in the world, with a GDP per capita of only $253 [49], and just over 50% of the population living below the poverty line [50]. The literacy rate in people aged 15 years and older is 65%, but is higher in men (74%) than women (57%). According to the 2010 Malawi Demographic health survey, 19% of women and 11% of men had received no formal education. Only 17% of women and 26% of men had completed primary school [51]. Seventy-two percent of households have access to improved sanitation facilities; and 79% have access to an improved water source, although only 3% have piped water into their dwelling [52].

Between the years 2000 and 2012, life expectancy at birth increased from 45 years to 59 years. However, healthy life expectancy is only 50 years, and 45% of the population are under the age of 15 years (figure 5) [48]. Under-five mortality remains high at 68 per 1000 live births [53].

Figure 5. Population pyramid for Malawi, 2011. [52]



Malawi spends 8.4% of its total GDP on health, but The Ministry of Health still relies on external donors such as USAID, The Global Fund, and PEPFAR to provide 50% of its funding. Despite this support, per capita expenditure on health is still less than $20 per annum, and there are only 0.2 physicians per 10,000 people (compared to 27.7 in the UK) [54].

The public health system in Malawi is four tiered, and consists of community, primary, secondary and tertiary care levels. At the community level, care is provided by Health Surveillance Assistants. Primary care is accessed through a large network of health centres and clinics. Twenty one district hospitals provide secondary care, and tertiary services are available at four central hospitals – in Lilongwe, Blantyre, Mzuzu and Zomba.

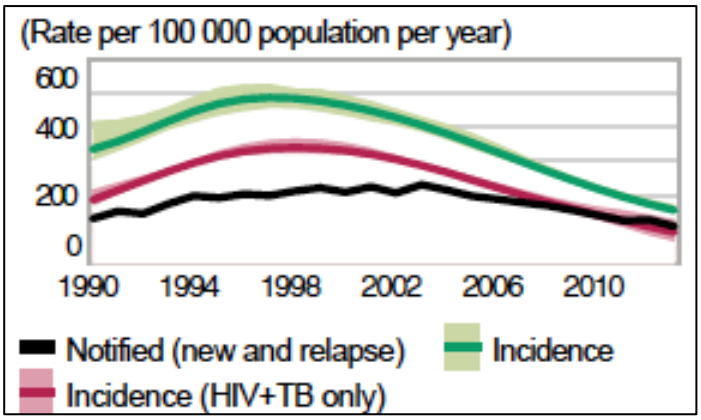
The HIV prevalence in Malawian adults aged 15-49 years is 10.3%, and HIV remains the leading cause of death, killing over 48,000 people in 2012 [55]. However, the number of new infections has been slowly declining since 2000, and it is estimated that 69% of those eligible for ART are on treatment [55]. HIV care is co-ordinated centrally using standardised treatment regimens. When ART was initially rolled out in 2004, a fixed dose combination of Stavudine, Lamividine and Nevirapine was

used. This has since been replaced, first for patients on TB treatment and then for the whole population, with a once daily combination of Tenofovir, Lamivudine and Efavirenz [56].

1.4.2 Tuberculosis control in Malawi

The incidence of TB in Malawi in 2013 was 156 per 100,000 persons, the lowest it has been for over three decades (figure 6) [4]. Due to the increase in population size however, this still amounted to nearly 20,000 case notifications. According to official reports, it is estimated that the TB case detection rate is 70%, although a recent prevalence survey is likely to demonstrate significantly lower case detection rates (unpublished data from Malawi NTP). HIV status is known in 92% of patients with TB, and the HIV prevalence amongst TB patients is 56%. A major contributing factor to the decline in TB incidence seen in figure 6 was presumably the country-wide roll out of ART in 2004. An initial increase in TB notifications was likely due to better detection of TB through scale up of ART services, but the gradual decline in incidence is most probably ascribed to the protective effect of ART [57]. Other factors which may also have contributed include improved diagnostics and improved socio-economic situation of the population. Currently, 88% of HIV positive TB patients are on ART, and 90% are prescribed cotrimoxazole preventive therapy.

Figure 6. TB incidence in Malawi. WHO Country profile 2014



A nation-wide survey conducted in Malawi between 2010-2011 demonstrated a very low prevalence of TB drug resistance (table 2). Only 0.4% of new patients and 4.8% of patients starting retreatment were found to have MDR-TB. 93.3% of new patients were infected with a strain of *M. tuberculosis* which was sensitive to all first-line drugs [58].

Table 2. Drug resistance profiles of MTB isolates in Malawi, 2010-2011

Resistance	Isolates from new cases ($n=1196$)		Isolates from retreatment cases ($n=581$)	
	No.	% (95% CI)	No.	% (95% CI)
Fully sensitive	1116	93.3 (91.7–94.7)	470	80.9 (77.5–84.0)
Any resistance[a]				
R	9	0.8 (0.4–1.4)	38	6.5 (4.7–8.9)
H	38	3.2 (2.3–4.3)	66	11.4 (8.9–14.2)
E	6	0.5 (0.2–1.1)	18	3.1 (1.9–4.9)
S	50	4.2 (3.1–5.5)	49	8.4 (6.3–11.0)
Multidrug resistance	5	0.4 (0.1–1.0)	28	4.8 (3.2–6.9)
RH	2	0.2 (0.0–0.6)	13	2.2 (1.2–3.8)
RHE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
RHS	1	0.1 (0.0–0.5)	6	1.0 (0.4–2.2)
RHES	2	0.2 (0.0–0.6)	8	1.4 (0.6–2.7)
Other forms of resistance	75	6.3 (5.0–7.8)	83	14.3 (11.5–17.4)
R only	3	0.3 (0.1–0.7)	9	1.5 (0.7–2.9)
H only	22	1.8 (1.2–2.8)	32	5.5 (3.8–7.7)
E only	2	0.2 (0.0–0.6)	4	0.7 (0.2–1.8)
S only	35	2.9 (2.1–4.1)	30	5.2 (3.5–7.3)
RS	1	0.1 (0.0–0.5)	0	0.0 (0.0–0.6)
RE	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)
HE	1	0.1 (0.0–0.5)	2	0.3 (0.0–1.2)
HS	10	0.8 (0.4–1.5)	3	0.5 (0.1–1.5)
ES	1	0.1 (0.0–0.5)	1	0.2 (0.0–1.0)
HES	0	0.0 (0.0–0.3)	1	0.2 (0.0–1.0)

The declining TB incidence, low prevalence of primary drug resistance, and >85% successful treatment completion in new patients indicate the strength of the Malawi National TB Control Programme. The NTP has historically administered a vertical programme, implementing the WHO recommended DOTS strategy since

1984 [59]. In line with the Ministry of Health's Sector Wide Approach to health development, the NTP began a process of decentralisation in 2005, aiming to increase equity in access to TB care [60]. There are currently 276 smear microscopy stations, and 247 registration centres across the country (data from Malawi NTP).

1.4.3 Retreatment tuberculosis in Malawi

Of the 19,539 TB notifications in Malawi in 2013, 2249 (11.6%) patients were prescribed retreatment regimen. Only 669 (29.7%) of these had microbiologically confirmed disease and were categorised as 'relapse' [4]. NTP policy states that all patients starting retreatment should have a sputum sample sent to the Central Reference Laboratory in Lilongwe for drug sensitivity testing, and, where available, GXP should be performed locally. But in 2013, sputum samples were analysed for rifampicin or multidrug-resistance in only 20% of patients who received retreatment [4]. All patients are managed with the standard WHO Category II retreatment regimen [61]. During the first 60 days of treatment, patients are admitted to their local district hospital in order to facilitate the administration of daily streptomycin injections. Despite a relatively well run TB control programme in Malawi, of previously treated cases in 2013 (excluding relapse) only 57% had successful clinical outcome on retreatment regimen [4].

1.5 Clinical outcomes on TB retreatment regimen: A systematic review

1.5.1 Background

In 1991 the World Health Assembly set a global target to cure of 85% of patients who receive treatment for TB and are sputum smear positive [62]. This was based not only on the implications for improving clinical outcomes in individual patients, but also on the potential for successful treatment to reduce further transmission, and therefore the number of new TB infections [63]. Millennium Development Goal number six is to "combat HIV/AIDS, malaria and other diseases." Encompassed in

this goal, two indicators relate specifically to TB: the "prevalence and death rates associated with tuberculosis" (indicator 23), and the "proportion of tuberculosis cases detected and cured under DOTS" (indicator 24) [64]. The Stop TB Partnership endorsed these indicators, and targets set by the Stop TB Strategy state that "national programmes around the world must not only reach at least 70% case detection and 85% treatment success, but also implement a wider range of activities", including by 2015 a reduction of TB disease prevalence and deaths by 50% relative to 1990 levels [65]. 'Success' in TB treatment is defined as the sum of all patients cured and treatment completed (table 3).

Table 3. WHO definitions of treatment outcomes for TB patients [66]

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative
Treatment failed	A TB patient whose sputum or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit
Treatment success	The sum of *cured* and *completed*

In recent years, great steps have been taken to meet these targets. Globally in 2011, 87% of new cases successfully completed treatment [35]. In Malawi, TB incidence has been slowly falling since the mid 2000s, and the proportion of patients being cured has been steadily increasing. However, rates of successful treatment are consistently lower in patients prescribed retreatment regimen.

According to The Global TB Report 2013, in the Africa region the treatment success rate was 82% in new smear positive patients and 76% in new smear negative/extra-pulmonary patients, but only 68% in patients undergoing retreatment [35]. According to official figures, in Malawi in 2010, 86% of new smear positive patients were cured, compared to only 77% of patients who were smear positive and on retreatment regimen [35], but data published in the medical literature from Malawi and other countries suggest that overall success rates in patients on retreatment regimen may be even lower.

A metanalysis of studies evaluating outcomes in patients who were retreated for TB identified only 6 cohort studies that reported outcomes in patients on TB retreatment regimen [67]. These studies demonstrated failure rates of between 0% and 27% in patients who were infected with a fully sensitive strain of MTB, but in patients with isoniazid monoresistance and mixed or unknown resistance patterns, failure rates were even higher at 18-44% and 9-45% respectively. This metanalysis only included those patients with microbiologically confirmed TB, and therefore excluded a large number of patients prescribed retreatment regimen who were smear and/or culture negative, and in whom outcomes were therefore likely to be even worse. A study conducted in Malawi that retrospectively examined operational data collected by the National TB Control Programme between January 2006 and December 2008 demonstrated that amongst all types of patients prescribed retreatment regimen, only 66% had a successful treatment outcome [68]. The remainder were lost to follow up (20%), died (11%), transferred out (2%) or failed treatment (1%).

The next section of the thesis describes a systematic review of the literature which was performed in order to get a more complete picture of the clinical outcomes on TB retreatment regimen, including both microbiologically confirmed and unconfirmed cases. This provided the opportunity to examine in more detail outcomes in different groups of patients (data not provided in the annual Global TB report), and to begin to consider possible factors which may be associated with poorer outcomes.

1.5.2 Objectives

The objective of this review was to describe the clinical outcomes in patients who receive WHO Category II retreatment regimen for Tuberculosis, and begin to address some of the gaps in our understanding of why treatment outcomes are poor.

The review aimed to answer 4 specific questions:

1. What is the proportion of patients who successfully complete retreatment regimen for Tuberculosis?
2. Does the proportion of patients who successfully complete TB retreatment regimen differ by TB category?
3. Does the proportion of patients who successfully complete TB retreatment regimen differ by HIV status?
4. What is the proportion of patients infected with an isoniazid resistant strain who successfully complete TB retreatment regimen?

1.5.3 Methods

1.5.3.1 Search strategy

Medscape, Embase and Scopus databases were searched using the terms listed in table 4. In addition a manual search of the journal 'Public Health Action' was performed, as it was a relatively new journal not yet fully referenced, and was identified as likely to publish relevant manuscripts. Finally, reference lists of the identified studies were examined for further relevant publications.

Table 4. Search criteria

	MEDSCAPE	SCOPUS	EMBASE
1	Tuberculosis (MeSH)	Tuberculosis	Tuberculosis
2	Retreat*	Retreat*	Retreat*
3	(Category II)	(Category II)	(Category II)
4	(Category 2)	(Category 2)	(Category 2)
5	#2 OR #3 OR #4	#2 OR #3 OR #4	#2 OR #3 OR #4
6	#1 AND #5	#1 AND #5	#1 AND #5
7	Filter Human	Filter English	Filter English
8	Filter English	From 1991	From 1991
9	From 1991		

1.5.3.2 Study selection

Studies which met the following criteria were included in the review:

1. Retrospective and prospective cohort studies or clinical trials reporting on clinical outcomes in patients prescribed TB WHO Category II regimen.

Studies which met the following criteria were excluded from the review:

1. Studies which report on patients receiving regimens for retreatment other than the WHO Category II retreatment regimen.
2. Studies which do not use standard WHO definitions for reporting TB outcomes i.e. 'cured', 'complete', 'failed', 'died', 'lost to follow-up', 'not evaluated'.
3. Reports of outcomes in patients on treatment for MDR-TB.
4. Papers reporting outcomes in patients registered prior to 1991 as this was the date the standard retreatment regimen was devised.

After removal of duplicates, the selection of articles for review was performed in three stages: study titles, then abstracts and finally full texts of manuscripts were reviewed. Two reviewers (DBC and JM) assessed manuscripts independently (see acknowledgements table on page v), and where discrepancies arose consensus was reached by discussion between the two reviewers and a third, independent

reviewer (SBS).

1.5.3.3 Data extraction and quality assessment

Data were extracted and entered directly into a standardised excel spreadsheet. Data extracted included details of the study design, setting, population characteristics, treatment regimens, reporting definitions, number of study participants, and details of outcomes, including, where possible, outcomes for different subgroups including tuberculosis category, HIV status and isoniazid sensitivity pattern. The sputum smear status of included patients was also noted. All studies reporting on patients receiving retreatment regimen were included, regardless of microbiological diagnosis. Any cohort that recruited consecutively treated patients was included.

1.5.3.4 Output definitions

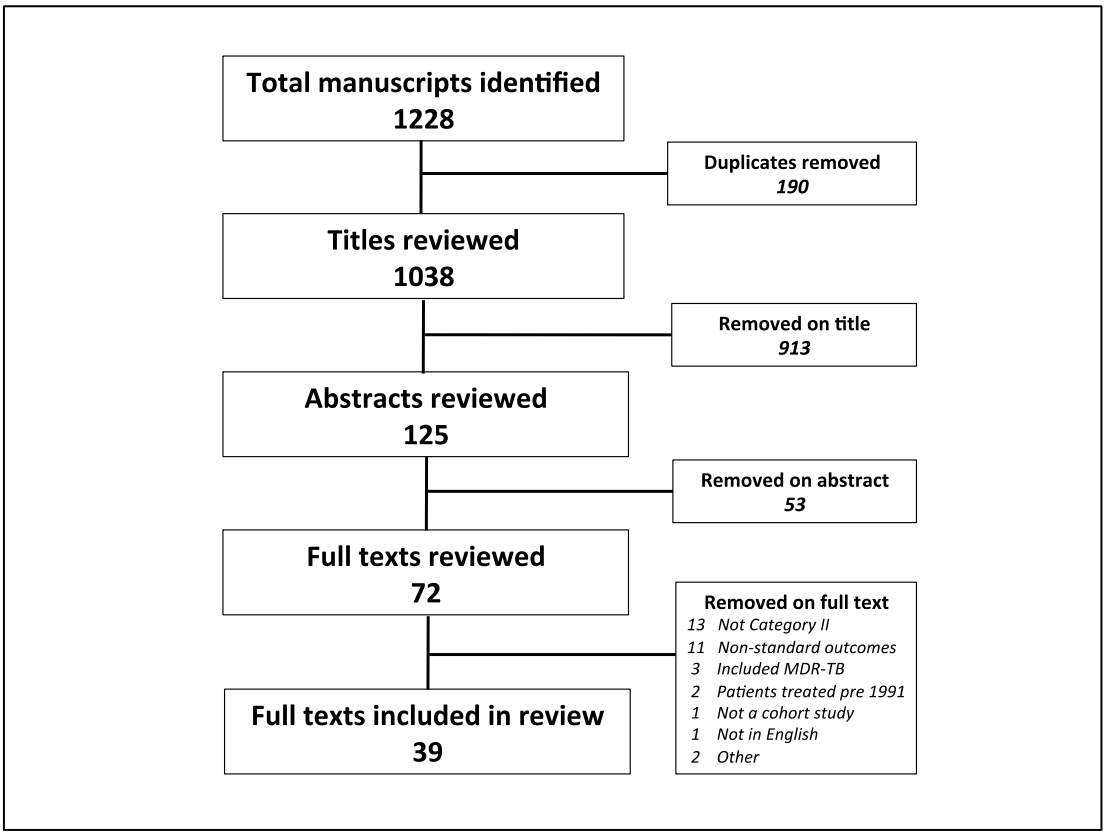
The specific endpoint of interest was the proportion of patients in whom an outcome of 'treatment success' was recorded. Treatment success is a composite of 'cured' and 'completed'. 'Cured' is defined as being smear negative at the end of treatment having started smear positive. 'Completed' is defined as finishing a course of treatment, but not meeting the criteria for cure. Data were extracted to determine the proportion of patients who were classified as cured, completed, died, lost to follow-up, failed, or not evaluated in each study (see table 3).

1.5.3.5 Data synthesis and analysis

The proportion of patients successfully completing retreatment regimen was calculated for each study. In accordance with WHO reporting standards, all patients registered for retreatment were included in the analysis. As such, patients whose final outcome was 'not evaluated' (including 'transferred out' and 'unknown') were included in the denominator. Extracted data was transferred into STATA version 12 for statistical analysis.

1.5.4 Results

Figure 7. Summary of study review and selection



1.5.4.1 Study selection

The results of the literature search are presented in figure 7. In total, 39 full text manuscripts met the inclusion criteria and were included in the review. Characteristics of the included manuscripts are outlined in table 5. The majority of studies were retrospective cohorts based on analysis of routinely collected data in local or national tuberculosis registers. There were only six studies that collected data prospectively, and only two of those were with the specific intention of examining outcomes on retreatment regimen [69, 70]. The majority of studies were conducted in Asia, predominantly India, or Africa.

1.5.4.2 Overall outcomes on retreatment regimen

The proportion of patients successfully completing retreatment regimen ranged from 27% - 92%. There was significant heterogeneity between studies (I^2 = 0.95), which precluded calculation of a pooled estimate. The recognised target for successful treatment in new smear positive patients is 85%, and only 2/39 (5%) of identified studies in retreatment met this target. The treatment success rate was less than 75% in 29/39 (74%) of studies, and less than 50% in 4 studies.

Table 5. Characteristics of studies included in the review

Reference *	Country	Study design	n	% Success	Population under study
Studies conducted in Asia					
Abeygunawardena, 2014 [71]	Sri Lanka	RC	160	0.82	All patients registered at a district chest clinic
Bam, 2007 [72]	Nepal	RC	118	0.92	Smear positive patients being treated for TB at refugee camps
Becx-Bleumink, 1999 [73]	Indonesia	PC	239	0.87	Smear positive patients prospectively enrolled in a pilot of ambulatory treatment
Burugina Nagaraja, 2011 [74]	India	RC	202	0.34	Patients from TB registration centres in 7 districts who had failed treatment
Chandrasekaran, 2007 [75]	India	RC	699	0.43	Smear positive patients from all TB registration centres in 1 district
Chughtai, 2013 [76]	Pakistan	RC	12656	0.78	All patients registered for treatment of pulmonary TB across the country
Deepa, 2013 [77]	India	RC	1077	0.67	Smear positive patients registered at all TB centres in 1 state
Halim, 2006 [78]	Indonesia	RC	107	0.70	All patients registered at a central hospital
Kumar, 2010 [79]	India	RC	133	0.64	All patients registered at centres in 1 district
Kumar, 2014 [80]	India	PC	38	0.55	All HIV positive patients treated for failure, relapse or default at a research centre
Mehra, 2008 [81]	India	RC	517	0.70	Patients treated for failure and relapse TB at a single urban chest clinic
Mukherjee, 2009 [82]	India	RC	234	0.68	Smear positive patients registered at a regional TB unit
Mukhopadhyay, 2011 [83]	India	RC	140	0.69	All patients registered 2 TB units in 1 district (1 urban, 1 rural)
Pardeshi, 2007 [84]	India	RC	507	0.66	Smear positive patients registered in 1 district
Sarpal, 2014 [85]	India	RC	545	0.81	All patients registered in 1 district
Sisodia, 2006 [86]	India	RC	2215	0.74	Smear positive patients registered in 4 districts
Srinath, 2011 [87]	India	RC	5365	0.76	All patients registered in 1 state
Vasudevan, 2014 [88]	India	RC	133	0.67	All patients registered in 1 district
Win, 2012 [89]	Myanmar	RC	3643	0.73	All patients registered across the country

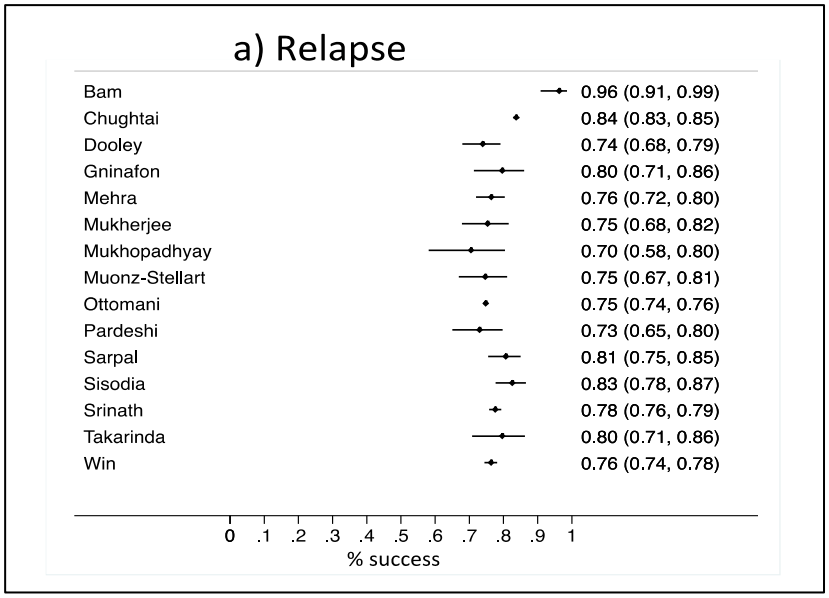
Studies conducted in Africa					
Akpabio, 2011 [90]	South Africa	RC	388	0.27	All patients with pulmonary TB registered at a regional TB hospital
Bohler, 2005 [91]	Sudan	RC	62	0.68	Smear positive patients registered at 5 TB management units in IDP camps
Bachmann, 2010 [92]	South Africa	CT	1385	0.62	All patients prospectively enrolled into the PALSA trial
Berhe, 2012 [93]	Ethiopia	RC	22	0.64	Smear positive patients registered at 10 rural & 5 urban districts
Dooley, 2011 [94]	Morocco	RC	291	0.73	Smear or culture positive patients registered at 9 urban TB clinics
Gninafon, 2004 [95]	Benin	RC	236	0.78	Smear positive patients registered at a large urban referral hospital
Ige, 2011 [96]	Nigeria	RC	127	0.74	All patients starting treatment at a University Hospital
Jones-Lopez, 2011 [70]	Uganda	PC	288	0.77	Smear positive patients treated as inpatients at a TB referral centre
Munoz-Sellart, 2010 [97]	Ethiopia	RC	338	0.66	All patients registered at 7 health centres
Nakanwagi-Mukwaya, 2013 [98]	Uganda	RC	105	0.46	All relapse, failure and default patients registered at 3 regional referral hospitals
Ottmani, 2006 [99]	Morocco	RC	14635	0.71	All bacteriologically confirmed cases registered across the country
Salaniponi, 2003 [100]	Malawi	RC	741	0.65	Smear positive patients registered at non-private health facilities
Takarinda, 2012 [101]	Zimbabwe	RC	225	0.72	All patients registered in 1 district
Tweya, 2011 [102]	Malawi	RC	411	0.67	All patients registered across the country
Wahome, 2013 [103]	Kenya	RC	46	0.61	All health care workers working at a referral hospital
Studies conducted in other regions					
Espinal, 2000 [104]	Multicentre	PC	876	0.57	Survey of DR-TB in Dominican Republic, Hong Kong, Italy, Russia, Korea & Peru
Furin, 2012 [105]	Georgia	RC	6633	0.58	All patients registered for TB treatment across the country
McGreevy, 2012 [106]	Haiti	RC	153	0.78	All patients registered at a TB-HIV referral centre
Ponce, 2012 [107]	Peru	CT	111	0.71	Smear positive patients registered in 3 districts
Sevim, 2002 [108]	Turkey	RC	47	0.83	Relapse and default patients registered at 1 referral clinic

RC retrospective cohort
PC prospective cohort
CT clinical trial
*Studies are listed in alphabetical order by author name

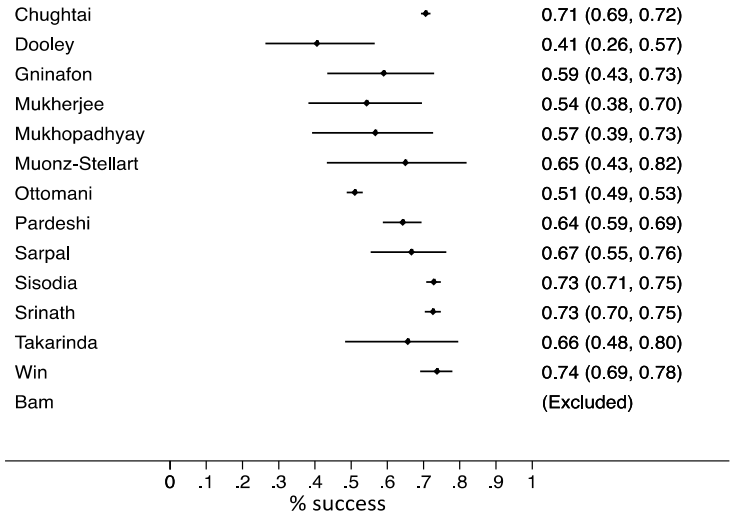
1.5.4.3 Outcomes on retreatment regimen by category

Figure 8 shows treatment outcomes by TB retreatment category. The mean successful completion rate in patients with TB relapse was 70% or above in all studies, and confidence intervals around these estimates tended to be small (figure 8a). On the other hand, there was a lot more variation in the outcome for patients registered as having returned to treatment after default or having failed treatment. Notably, very few studies specifically report outcome in in patients registered as 'other'. The rate of successful treatment in this group varied considerably - from 61% to 84%.

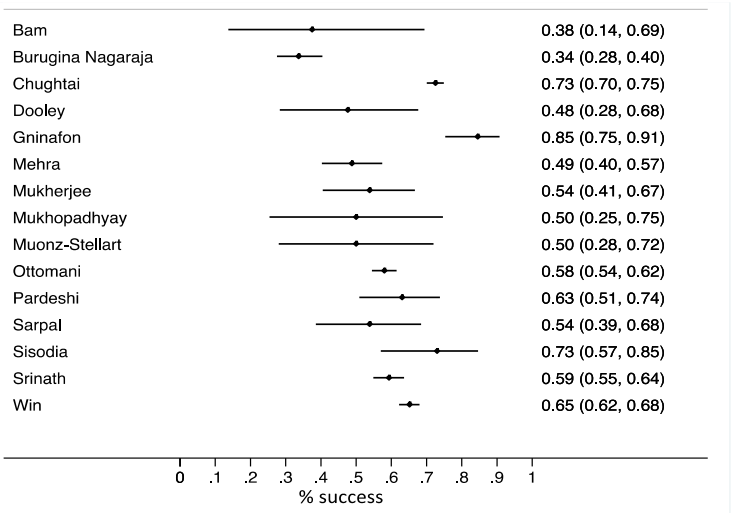
Figure 8. Treatment outcomes by TB retreatment category



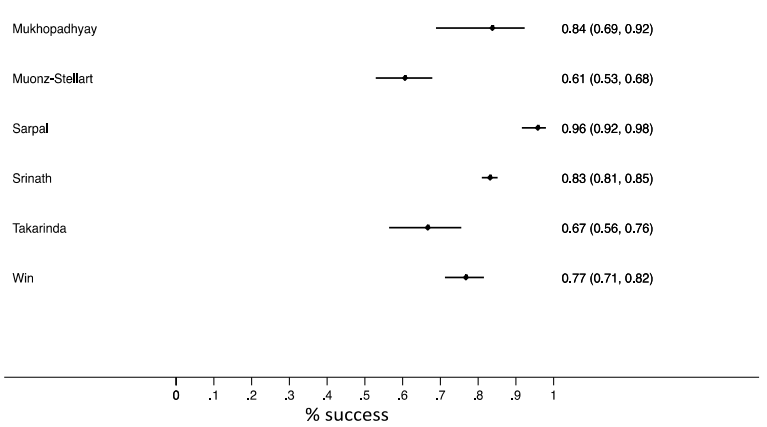
b) Treatment after default



c) Failure



d) Other previously treated



1.5.4.4 Outcomes on retreatment by HIV status

Only five studies compared outcomes on retreatment between HIV positive and HIV negative patients (table 6). One further study from India reported 55% successful outcome in a cohort of 38 patients, all of whom where HIV positive [80]. Of the studies comparing outcomes in HIV positive and HIV negative patients, two were conducted in African countries with generalised HIV epidemics (Uganda and Zimbabwe); one in Haiti (HIV prevalence <2%); one in Indonesia (HIV prevalence 0.5%); and one in India (HIV prevalence <0.5%). In four out of the five studies, outcomes were worse in HIV-infected patients. In the one study that reported higher success rates in HIV positive people, the number of HIV negative patients was very small. Jonez-Lopez et al report an adjusted odds ratio of 2.16 (1.01-4.61) for unsuccessful outcome in HIV positive patients, with factors associated with death in HIV being CD4 count <50 cells/ml, no ART, and Karnofsky score <70 [109]. In the study by McGreevy et al, follow up data demonstrated that only 46% of HIV positive patients remained alive, in ART care and TB-free after a median of 36 months of follow up [110].

Table 6. Retreatment outcomes by HIV status

Study	Success in HIV positive % (95%CI)	Success in HIV negative % (95%CI)
Ige [96]	27/42 0.64 (0.49-0.79)	67/83 0.81 (0.73-0.89)
Jonez-Lopez [109]	103/140 0.74 (0.67-0.81)	118/148 0.80 (0.74-0.86)
McGreevy [110]	41/56 0.73 (0.61-0.85)	79/97 0.81 (0.73-0.89)
Srinath [87]	38/55 0.69 (0.57-0.81)	97/111 0.87 (0.81-0.93)
Takarinda [101]	101/135 0.75 (0.68-0.82)	15/21 0.71 (0.52-0.90)

1.5.4.5 Outcomes on TB retreatment according to isoniazid sensitivity pattern

Outcomes were reported in four studies that had data on isoniazid sensitivity, which amounted to a total of only 217 patients. Three of the four studies were conducted in India, and in these the prevalence of isoniazid resistance ranged from 12% - 28%. The largest of the studies specifically aimed to compare outcomes in patients with and without isoniazid resistance, and found that 44% of those with isoniazid resistance had poor treatment outcomes, compared to 31% of those infected with an isoniazid sensitive strain (aRR 1.46; 95% CI 1.19-1.78) [111].

Table 7. Retreatment outcomes with isoniazid resistance

Study	Success in INH resistance % (95%CI)
Burugina-Nagaraga [74]	5/46 0.11 (0.04-0.24)
Deepa [111]	80/144 0.56 (0.47-0.64)
Kumar [80]	3/4 0.75 (0.19-0.99)
Salaniponi [112]	18/23 0.78 (0.56-0.93)

1.5.5 Discussion

This review demonstrates that rates of treatment completion using the WHO Category II regimen for retreatment of tuberculosis are consistently lower than the 85% treatment success rate target across populations in various settings, regardless of HIV status, TB category, or isoniazid resistance pattern. There were only 2 studies which achieved greater than 85% treatment success. One of these was conducted in a refugee camp - a situation in which there was likely to be little movement of people who were living in a well defined space, and for who follow up may therefore have been easier. The other was a study of ambulatory care, suggesting that this was a particularly well group of patients.

Whilst clinical outcomes on TB retreatment regimen are persistently poor, it is not entirely clear why this is so. It is often assumed that the low cure rates are due to the increased prevalence of drug resistance in this group, which is associated with higher rates of treatment failure, and relapse [113].

A recent survey in Malawi reported that in only 6.7% of new TB patients was any form of resistance to first line anti-tuberculous drugs identified, including 0.4% who had MDR-TB [58]. In comparison, 19.1% of people undergoing retreatment had drug resistant strains of MTB isolated from sputum, with 4.8% having MDR-TB. However, an alternative interpretation of these data would conclude: “80% of patients undergoing TB retreatment in Malawi are infected with a fully sensitive strain of MTB”. This may suggest that in areas of low MDR-TB prevalence, drug resistance does not explain all of the unsuccessful treatment outcomes, and that there may be other factors accounting for some of the failure to complete retreatment. It is important to consider other factors contributing to poor outcomes because if any are amenable to intervention, it may be possible to develop additional approaches to improving management.

Firstly, it may be that some patients do not have TB at all, in which case the misdiagnosis will result in treating for TB and not the true underlying disease. Whilst

there have been several studies examining the alternative causes of smear negative TB in patients presenting with a first episode of TB, there exist very few data exploring this issue in patients being retreated [114, 115]. Secondly, given the fact that these patients are having recurrent episodes of TB, it is possible that other co-morbid conditions, which both predispose to TB and are associated with worse outcomes, are prevalent in this group. For example, it has been observed by doctors on the TB ward at QECH that there is a particularly high HIV prevalence and a large burden of lung disease amongst patients being retreated (personal communication Prof H. Mwandumba, MLW). Thirdly, because of prolonged treatment duration and the addition of streptomycin to the retreatment regimen, adverse events may be common and result in discontinuation or interruption of treatment. Finally, this longer and more demanding regimen may be associated with poor adherence and increased rates of default from treatment. The following sections review some of these factors which may account for poor clinical outcomes in TB retreatment.

1.6 Co-morbidity in patients with Tuberculosis

Tuberculosis has been associated with a number of other medical conditions, such as HIV, diabetes and occupational lung disease. Very little is known specifically about co-morbidity in patients being treated for recurrent TB. However, the next sections review the literature concerning co-morbidity in patients with tuberculosis in general, as a background to understanding the potential factors which may play a role in those with recurrent TB. It may be suspected that co-morbid medical conditions which predispose people to a single event of tuberculosis may be even more prevalent in those with repeated episodes.

1.6.1 Tuberculosis and HIV

Between 1990 and 2008 there was a 40% increase in the number of cases of tuberculosis globally, which was largely attributable to rises in sub-Saharan Africa and driven by the rising epidemic of HIV [116, 117]. By 2013, an estimated 1.1 million (13%) of the 9 million people who developed tuberculosis worldwide were

HIV positive, and there were 360,000 deaths in HIV positive people, accounting for one third of all tuberculosis deaths and making tuberculosis the leading cause of death amongst people infected with HIV [4]. Currently in the African Region, where the burden of HIV is greatest, 41% of all notified cases test positive for HIV, and in Malawi that proportion is even higher at 56% [4]. The incidence rate of tuberculosis has been estimated to be 20-36 times higher in HIV positive people compared to HIV negative people, depending on the characteristics of the local HIV epidemic (table 8).

Table 8. Estimated incidence rate ratios for tuberculosis in HIV positive people

HIV epidemic situation	TB Incidence rate ratio
Generalised:	
Prevalence of HIV consistently >1% in pregnant women	20.6 (15.4-27.5)
Concentrated:	
Prevalence of HIV consistently >5% in at least 1 subpopulation and <1% among pregnant women in urban areas	26.7 (20.4-34.9)
Low-level:	
Prevalence of HIV not consistently >5% in any subpopulation	36.7 (11.6-116)

Adapted from Getahun et al [118]

HIV increases the risk of reactivating latent tuberculosis infection, as well as increasing the risk of rapid progression of tuberculosis disease following primary infection or reinfection [119]. Unlike other opportunistic infections, the risk of tuberculosis is increased throughout the course of HIV infection, although risks are highest in those with low CD4 counts [120-123]. HIV infection results in impaired innate and adaptive immune responses to tuberculosis, and ultimately leads to the inability to contain mycobacteria due to poor granuloma formation [124, 125]. The HIV virus affects the host immune response to tuberculosis in a number of ways, including manipulating macrophage function; destroying CD4+ T cells within granulomas; and reducing the ability of T-cells to produce IFN-γ which plays a

crucial role in controlling the response to M. tuberculosis [126]. The complexity of the relationship between these two infections is heightened by the fact that tuberculosis can also affect the course of HIV disease [127]. Tuberculosis has been shown to double mortality in HIV infection, regardless of CD4 count [128]; and to increase both HIV viraemia and viral heterogeneity [129].

Altered immune responses to tuberculosis frequently result in atypical clinical presentation in patients infected with HIV. HIV positive people more often present with smear negative [130], extra-pulmonary [131] and severe disseminated forms of tuberculosis [132], particularly as CD4 counts fall [133]. Classical radiological features such as consolidation or destructive, cavitatory disease are less common - in fact HIV positive people with confirmed pulmonary tuberculosis frequently have entirely normal chest x-rays, particularly if they are severely immunosuppressed [134-137]. Extrapulmonary and paucy-bacilliary features mean that the diagnosis of tuberculosis in those who are HIV positive is an even greater challenge. The lack of sensitivity of diagnostic tools has led to the development of a number of screening algorithms for detecting tuberculosis in HIV positive people, with variable success [138-140]. Diagnosis often remains delayed or missed entirely, potentially contributing to poor outcomes.

Once diagnosed, the treatment of new or recurrent tuberculosis is the same regardless of HIV status. However, because of the interplays between tuberculosis, HIV, and the drugs used to treat the two infections, the management of co-infected patients is complex. Although there are a lack of data specifically regarding interactions between ART and the Category II regimen, information about the significant issues regarding concomitant administration of anti-tuberculous drugs and ART can be extrapolated to patients on retreatment regimen as all four first line drugs which constitute short course chemotherapy are included in the regimen. Drug interactions can result in increased risks of side effects, particularly hepatotoxicity [141]; and the enzyme inducing properties of rifampicin can reduce the concentrations of anti-retroviral drugs putting patients at risk of developing ART resistance [142, 143]. Additionally, ART can be associated with tuberculosis related

Immune Reconstitution Inflammatory Syndrome (IRIS) [144, 145], and the high pill burden which comes with multiple medications may affect adherence to both treatments [146]. However, the benefits of HIV treatment and the associated reduction in opportunistic infections outweigh these risks, and early ART has been shown to reduce mortality during tuberculosis treatment particularly in those with very low CD4 counts [147-149], such that early antiretroviral treatment is now recommended for all HIV positive patients with active tuberculosis [150].

The potential link between drug resistant tuberculosis and HIV is still debated. In a systematic review of published studies, Suchindran et al reported that most studies from North America showed an association between MDR-TB and HIV, but not a single study in Africa demonstrated such an association and results from other regions were conflicting [151]. In this and other studies, the increased risk seems to be attributable to an increased risk of primary, rather than acquired drug resistance [152]. Possible biological explanations for this include poor absorption of drugs from the gastrointestinal tract in those infected with HIV, leading to suboptimal plasma concentrations of drugs. Alternatively, as previously discussed, a high proportion of tuberculosis in HIV positive people is caused by primary infection, unlike in HIV negative people. Given the increasing prevalence of drug resistance, it is therefore possible that primary disease acquired from recent transmission is more likely to be drug resistant. Moreover, HIV positive people are likely to be at increased risk of environmental exposure to drug resistant strains, for example through frequent contact with health care services. This was demonstrated by the extremely high prevalence of HIV in the infamous nosocomial outbreak of XDR-TB in Kwazulu-Natal [153].

Multiple studies have shown the devastating effects of co-infection with HIV and MDR-TB on treatment outcomes. Mortality estimates range between 32% and 72% on treatment, and are consistently higher than in HIV uninfected people treated for MDR-TB [154-156]. Despite the conflicting evidence about the role of HIV as a risk factor for MDR-TB, the implications for diagnosis, treatment and outcomes in co-

infected people are such that the management of MDR-TB in HIV deserves particular attention [157, 158].

1.6.2 Post Tuberculosis Lung Disease (PTLD)

Post tuberculosis lung disease (PTLD) is common and respiratory sequelae of tuberculosis include airways disease, parenchymal lesions and pleural disease [159, 160].

The patterns of abnormality seen in pulmonary function testing after tuberculosis are variable, and have almost exclusively been described only in patients presenting with a first episode of TB. Restrictive defects at the beginning of TB treatment have been reported to persist, resolve or become obstructive over time [161]. Much research has focussed on the association between tuberculosis and chronic airways obstruction (CAO), with a number of retrospective and cross sectional studies reporting an association between CAO and a history of tuberculosis [162-165]. The mechanisms by which tuberculosis can cause airways obstruction include direct damage to endobronchial structures resulting in local obstruction and fibrosis; extrinsic compression by enlarged lymph nodes; and parenchymal disease which results in reduced pulmonary compliance, peripheral airways collapse and subsequent air trapping [166].

The diagnosis of Chronic Obstructive Pulmonary Disease (COPD) is based on demonstrating CAO in the context of exposure to recognised risk factors [167], with smoking being the most common risk factor but exposure to biomass fuel also playing a role, particularly in developing countries [168]. TB is recognised as a risk factor for the development of COPD, but the higher rates of CAO after tuberculosis have been shown to persist after controlling for smoking [169-171], suggesting that tuberculosis is also an independent risk factor for CAO. In a systematic review of the association between tuberculosis and CAO, Allwood concludes that “it is debatable whether TB-associated CAO should be considered as part of the COPD spectrum, a distinct phenotype of COPD, or as an unrelated disease”[172].

Prospective studies have provided evidence for the effects of residual pulmonary impairment after an episode of TB on functional ability, morbidity and mortality. A prospective study in Indonesia which recruited 200 patients with pulmonary tuberculosis and 40 controls, reported the mean FEV1 was 92% of predicted in controls compared to 63% in cases at baseline, and 71% in cases after 6 months. Despite achieving 'successful' treatment outcomes, 27% of patients with tuberculosis still had moderate-severe impairment in pulmonary function and 57% still had respiratory symptoms at the end of treatment. Moreover, functional ability was markedly affected in patients with tuberculosis, and persisted to 6 months (6MWT 497m in controls, 408m in cases at baseline ($p<0.0001$), and 470m in cases at 6 months ($p=0.02$)) [173]. A similar study of 115 patients with tuberculosis found that 24.6% had persisting significant lung function impairment at the end of treatment, and that this was associated with both reduced exercise tolerance and quality of life [174]. In addition to significant impacts on morbidity, impaired lung function has also been shown to be associated with increased mortality [175, 176].

Bronchiectasis can be defined as "permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of micro-organisms and recurrent chronic infection" [177]. Infections are the most common cause of bronchiectasis amongst people with non-cystic fibrosis bronchiectasis [178]. The pathogenesis of bronchiectasis is thought to be explained by the vicious cycle of host mediated inflammatory response to foreign material and organisms causing damage to airways, which in turn results in abnormal mucous clearance and further bacterial colonisation [179]. The association between tuberculosis and bronchiectasis has been recognised since the 1800s [180], and the proportion of cases of bronchiectasis due to tuberculosis has been estimated at between 1% and 32% [166]. Extensive bronchiectasis can cause airflow obstruction; hence there is a significant overlap between bronchiectasis, CAO and tuberculosis [166, 181].

Tuberculous Destroyed Lung (TDL) is extensive, progressive destruction of the lung parenchyma secondary to tuberculosis [182], and can result in progressive dyspnoea, recurrent infections, decline in respiratory function and cor pulmonale

[183, 184]. TDL is associated with high morbidity from worsening breathlessness, repeated acute exacerbations and multiple hospital admissions. It also carries with it a high mortality with one study reporting a median survival of 39 months [185].
A well-recognised complication of PTLD is infection with the fungus Aspergillus. Aspergillus is a ubiquitous fungus which can cause a range of pathologies, but in PTLD is associated with Chronic Pulmonary Aspergillosis (CPA). There are various patterns of presentation of CPA [186]. Some patients present with rapid development of symptoms and consolidation with or without cavitation on imaging. More commonly, CPA presents with slowly evolving, single or multiple lung cavities that may or may not contain a fungus ball (aspergilloma). Less well recognised is the phenomenon of 'tracheobronchial aspergillosis' which causes only minimally invasive, local disease. A study in Uganda has shown that 60/200 (15%) post-TB patients have both chronic symptoms and x-ray changes consistent with CPA [187], and it has been estimated that in 2007 alone, 372 000 people globally developed CPA following an episode of tuberculosis [188].

1.6.3 Tuberculosis and diabetes

An association between tuberculosis and diabetes mellitus has been postulated since the early twentieth century [189]. Interest in the interaction between the two diseases has resurfaced recently, particularly since the projected epidemic of diabetes has come to light [190]. According to the International Diabetes Federation, the number of people with diabetes is set to increase from 387 million to 592 million by 2035, with over 75% of these people living in low and middle income countries [191].

There have been a number of reports demonstrating that co-affliction with tuberculosis and diabetes mellitus (TB-DM) is common, although all of these concentrate on the interaction amongst patients presenting with a first TB episode [192-195]. In 2008, Jeon et al published a systematic review of 13 observational studies which concluded that diabetes mellitus was associated with tuberculosis

(relative risk 3.11), however the majority of these studies were retrospective, many were based on self reported diagnoses, and none were conducted in Africa [196]. None the less, growing interest in the association resulted in The Union, The WHO Stop TB Department and the World Diabetes Foundation convening a joint consultation meeting in 2009 which highlighted the need for further efforts to combat the impact of TB-DM [197]. Although predictions based on diabetes prevalence and TB incidence forecast a large rise TB-DM in South Africa [198], primary data have only recently begun to emerge from the continent as a whole. Cross sectional studies have reported the prevalence of DM in groups of patients starting TB treatment, and there is a suggestion that this may be higher than in the general population [199, 200]. Only one case control study from the continent, conducted in Tanzania, has demonstrated that diabetes is associated with tuberculosis (OR 2.2, 95% CI 1.5-11.6), but this was dependent on HIV status, with no significant association shown in those who were HIV infected [201].

In addition to increasing the risk of tuberculosis, it is possible that diabetes affects the clinical presentation and course of TB, and that outcomes on TB treatment are worse in people who have diabetes. A metanalysis has reported that the risk of death during TB treatment is higher in patients with diabetes (RR 1.89), as is the risk of relapse (RR 3.89) [202]. It is unclear whether poorer outcomes are due entirely to TB related factors, or also to direct complications of diabetes and other associated morbidities, however there are some data to suggest that diabetes is linked with more severe TB disease. For example, a large study conducted in Taiwan prospectively enrolled over 1200 patients with culture positive Pulmonary TB and found that compared to patients without DM, those with TB-DM were significantly more likely to have opacity over the lower lung fields, extensive parenchymal lesions, and cavitatory disease [203]. Additionally, a number of studies have reported longer time to smear or culture conversion in patients with diabetes [204-206]. Of particular relevance in patients being retreated for TB is the possibility of an interaction between diabetes and drug resistant TB, although data so far do not support such an association [207, 208].

The pathological mechanism underlying the TB-DM association is likely to be multifactorial, involving multiple components of the host immune response. Defence against tuberculosis is dependent on both innate and adaptive immune responses [8, 10]; and diabetes is well known to result in impaired immune response to infection [209]. Examination of the direct immunological responses to tuberculosis in diabetes has highlighted the importance of impaired macrophage function and phagocytosis in both mouse models [210] and human studies [211]. Data also suggest that adaptive responses to tuberculosis are altered in individuals with diabetes, but changes in IFNγ responses to tuberculosis vary across studies [212].

1.6.4 Tuberculosis and Anaemia

Anaemia is common in patients with tuberculosis, with prevalence estimates ranging between 32% and 86% [213-216]. The pathogenesis of anaemia in tuberculosis is multifactorial, with components of both iron deficiency anaemia (which can resolve with iron supplementation) and anaemia of chronic disease, or 'anaemia of inflammation' (which can resolve on treatment for tuberculosis) [215, 217, 218]. The interaction between tuberculosis, anaemia and HIV is complex, as anaemia is common in both tuberculosis and HIV. However, it has been shown that anaemia is a strong independent predictor of tuberculosis amongst HIV positive people [219], and that anaemia is associated with HIV infection in patients with tuberculosis [220]. The presence of anaemia in tuberculosis is associated with reduced rates of sputum smear conversion at 2 months [214], as well as increased risk of recurrence [218], adverse drug reactions [221] and higher overall mortality [222, 223].

1.6.5 Tuberculosis and nutrition

It has long been recognised that under-nutrition is a key risk factor for the development of Tuberculosis. For example, much of the decline in tuberculosis incidence in industrialised countries prior to the introduction of anti-microbials has

been attributed to improved nutritional status of the population [224]. A systematic review of the literature has reported a reduction in tuberculosis incidence of 13.8% per unit increase in BMI [225]; and the relative risk of tuberculosis for people with under-nutrition has been estimated to be 3.2 (95% CI3.4-14.2)[226]. The risk is thought to be due to lack of both macro- and micro-nutrients, with deficiency in vitamin D being of particular importance [227]. A model which assumes that the goal to end hunger by 2035 is met, estimates that the global tuberculosis incidence would be reduced by 18% [228].

In addition to playing a role in the risk of developing tuberculosis, failure to gain weight during the course of tuberculosis treatment is a strong predictor of poor treatment outcome [229]. However, the benefits of nutritional supplementation alongside anti-tuberculous treatment are limited [230]. Nevertheless, because of the clear link between tuberculosis and under-nutrition, the WHO has published guidelines on 'Nutritional care and support for patients with tuberculosis,' which recommends that "an adequate diet, containing all essential macro-and micro-nutrients is necessary for the well-being and health of all people, including those with TB," therefore "nutrition screening, assessment and management are integral components of TB treatment and care."[231]

1.7 Toxicity of anti-tuberculous drugs

Adverse Drug Reactions (ADRs) are experienced in 5 – 40% of patients on first line anti-tuberculosis drug treatment, and vary according to clinical setting and definition [232-235]. In a prospective cohort of 430 patients on first line anti-tuberculous drugs, Yee et al report an overall incidence of 0.55 ADRs per 100 person months follow up, with reactions to pyrazinamide being the most common, followed by reactions to Isoniazid, Rifampicin and Ethambutol (1.48, 0.49, 0.43 and 0.07 events per 100 person months respectively) [233]. The frequency of ADRs is persistently reported to be higher in women, older people, and HIV positive people [233, 235, 236]. There are several implications of major adverse reactions to anti-

tuberculous drugs. Serious reactions may themselves result in significant morbidity and mortality [237, 238]. Additionally, discontinuation of treatment due to adverse events may result in periods of no treatment or suboptimal dosing, prolonged treatment duration and in some cases may ultimately require substitution with less potent, potentially more toxic second-line drugs.

The most common severe ADRs associated with anti-tuberculous treatment are skin reactions and hepatotoxicity; other side effects include gastrointestinal disturbance, isoniazid associated peripheral neuropathy, pyrazinamide associated arthralgia, and ethambutol associated optic neuritis [238]. However, as drugs are given in combination and have many overlapping toxicity profiles, it is often difficult to confidently establish which is responsible for a particular ADR. Drug Induced Liver Injury (DILI) is associated with rifampicin, isoniazid and pyrazinamide and causes hepatocellular necrosis with or without cholestasis [239]. In cases where the patient develops clinical hepatitis, or there is a significant rise in serum levels of transaminases and/or bilirubin, anti-tuberculous treatment must be stopped and reintroduced either stepwise or at full dose [240]. Shang et al describe a 9-fold increase in the risk of unsuccessful TB outcome in patients who develop hepatotoxicity, and a 2-fold increase in the risk of prolonged treatment [241].

Cutaneous adverse drug reactions (CADR) can be caused by all five of the first line anti-tuberculous drugs and usually develop within the first few months of treatment. The range of cutaneous manifestations encompasses a spectrum from mild rash to severe life threating reactions such as Steven's Johnsons Syndrome [242]. In severe cases of CADR, all anti-tuberculous drugs must be stopped and reintroduced, but patients offen suffer reintroduction reactions which can also be severe [243].

In areas of high HIV prevalence the interactions between HIV and TB, as well as the interactions between drugs used to treat them, makes the diagnosis and management ADRs even more complex. ADRs on anti-tuberculous drugs are more common in HIV infected people, with one study from South Africa reporting ADRs in

26.7% of HIV-infected people, compared to 13.3% of HIV-uninfected people [244]. A further study in the same country found that of 71 cases with TB-ART DILI, 39 were due to anti-tuberculous drugs, 12 to ART, and 20 to both. Overall 3-month mortality in this group was extremely high at 35% [245]. Risk factors for HIV positive people developing hepatotoxicity due to anti-tuberculous drugs have been shown to include low BMI, disseminated tuberculosis, low CD4 count and WHO stage IV HIV disease [246]. As well as DILI, the risk of CADRs has also been shown to be higher in HIV infected people [242, 247].

In addition to RHZE, patients prescribed retreatment regimen are exposed to the increased risks posed by toxicity from streptomycin. Streptomycin is an aminoglycoside antibiotic, and the nephrotoxic and ototoxic effects of this class of drug have been well described [248-250]. Aminoglycosides cause ototoxicity by destruction of the hair cells within the cochlear and vestibule. This leads to high frequency hearing loss and vestibular damage that are usually irreversible [251, 252]. Nephrotoxicity caused by aminoglycosides is due to necrosis of the proximal tubules, and, unlike ototoxicity, is usually reversible [253, 254]. Data concerning the long-term use of aminoglycosides in tuberculosis tend to be focussed on side effects of treatment for MDR-TB rather than streptomycin [255-259], and there is no information specifically regarding streptomycin toxicity in Africa. Nevertheless, the rate of aminoglycoside toxicity in patients on tuberculosis treatment seems to be high. A study of 110 patients in the Netherlands who were prescribed amikacin, kanamycin or streptomycin reported that 18% developed hearing loss, whilst 7.5% developed nephrotoxicity. Toxicity was associated with longer duration of treatment and larger total doses [260].

The high incidence and irreversibility of ototoxicity mean that hearing loss is likely to contribute the largest burden of morbidity related to aminoglycoside toxicity in the treatment of tuberculosis. Features of hearing loss in patients prescribed aminoglycosides for the treatment of MDR-TB have been summarised in a review by Seddon et al who report rates of ototoxicity ranging from 8-28% in studies which used standardised methods for assessing ototoxicity, and 1-50% where

unstandardised methods were used [261]. Limited data exist on risks of ototoxicity on streptomycin. A case series of patients from Brazil reported that 75% of patients on streptomycin had hearing loss, although no baseline assessments were performed [262]. Further data from a series in the USA demonstrated ototoxicity developed in 28% of patients who received streptomycin (compared to 56% on kanamycin and 59% on amikacin) [263]. Risk factors for the development of hearing loss on anti-tuberculous treatment are not well defined, although genetic mutations predispose a proportion of patients to streptomycin ototoxicity [264], and it is possible that HIV positive patients on treatment for MDR-TB are also at higher risk of developing hearing loss [265].

1.8 Models for the delivery of injectable anti-tuberculous drugs

In addition to poor clinical outcomes and high rates of medical co-morbidity, patients on retreatment regimen are faced with the problem of having to receive daily injections of streptomycin. This issue is also a problem for those being treated for MDR-TB who need injectable agents for even longer, usually eight months. Different approaches exist to delivering injectable drugs to patients who require them long term. Traditionally, patients are admitted to hospital in order to receive their treatment from a health care professional, but more recently community based approaches to delivering parenteral drugs have been developed for TB and other conditions.

1.8.1 Disadvantages of hospital admission for tuberculosis

1.8.1.1 Nosocomial transmission of infection

Hospital admission puts patients at risk of acquiring nosocomial infections. Health Care Associated Infections (HCAI) are linked with increased morbidity and mortality, prolonged admission times, and increased use of resources [266]. A recent review has reported the prevalence of HCAI in developing countries is 15.5 per 100 patients, which is significantly higher than proportions reported from Europe and

the US [267]. Few data exist on HCAI in Africa, however it appears that the prevalences of methicillin-resistant *S. aureus* and resistant enterobacteriaceae are increasing [268]. Factors associated with HCAI include prolonged use of invasive devices and antibiotics, high-risk procedures, immuno-suppression and insufficient application of isolation procedures [267]. Patients on TB retreatment admitted to hospital in settings such as Malawi are therefore at high risk of acquiring HCAIs, as the majority are HIV positive, they are all on prolonged antibiotics, and most are managed on open wards with shared facilities.

It also is well established that there are significant levels of TB transmission associated with health care facilities [269, 270]. Transmission occurs between patients, visitors and health care workers putting large numbers of people at risk of becoming infected. Of particular concern is the risk of transmission of MDR and XDR-TB, which was highlighted by the outbreak of XDR-TB associated with a health facility in South Africa [153]. It is therefore recommended that whenever possible, patients with MDR-TB are placed on active treatment and managed in the community [26, 271]. With this in mind, it is important to recognise that the highest burden of drug-resistant tuberculosis is amongst patients starting retreatment regimen. For these people to be admitted to hospital, a large reservoir of potentially infectious drug resistant TB is being created, particularly given the delays often associated with the diagnosis of drug resistance and institution of appropriate management [272, 273].

1.8.1.2 Social and economic effects on patients and households

Admission to hospital is associated with large economic burdens for patients and their families. Costs to users include direct costs of medical care, other out of pocket expenses such as food and transport, as well as lost earnings [33, 34]. Although TB care is provided free in Malawi, there are still many direct and indirect costs associated with diagnosis and treatment [274]. It is becoming increasingly recognised not only that households frequently incur catastrophic health costs as a result of tuberculosis, but also that these catastrophic costs can be associated with

poor clinical outcomes [275]. Due to these concerns, in 2013, the World Health Organisation set a target that no families would face catastrophic costs due to TB by 2030 [276]. Multiple studies have demonstrated higher user costs associated with facility-based management during the intensive phase of standard short course therapy (table 9).

Table 9. User costs of facility-based and community-based management during TB treatment

Reference	Setting	Cost per person of facility-based management (US$)	Cost per person of community-based management (US$)
Floyd et al [277]	South Africa	272	91.60
Floyd et al [278]	Malawi	228	95
Moalosi et al [279]	Botswana	720	551
Nganda et al [280]	Kenya	297	89
Okello et al [281]	Uganda	91	62
Wandwalo et al [282]	Tanzania	43	19

In many Sub-Saharan African countries, if a patient is admitted to hospital they are accompanied by a 'guardian' – a lay person, usually a family member or friend, who looks after them and provides much of their basic care including washing, dressing, feeding, collecting and often giving patients oral medications [283]. In effect, this often results in two adult members of a household being away from home, therefore unable to provide and care for the family, and having to rely on friends and family for help so that the financial burden of illness also becomes a social burden [284]. The psychological effects of prolonged admission to hospital have also been recognised, and data from a survey conducted on the TB ward at QECH demonstrated that 40% of patients screened positive for common mental health disorder or depression (data presented at Malawi College of Medicine Research Dissemination Conference 2007, Dr R. Stewart).

1.8.1.3 Financial burden on the health system

A number of studies have reported the high healthcare costs associated with hospital admission for TB treatment (table 10), and they have consistently demonstrated that it is more cost effective to manage patients in the community. The high costs of facility-based treatment are primarily due to the costs associated with in-patient admissions.

Table 10. Provider costs of facility-based and community-based management during TB treatment

Reference	Setting	Cost facility-based management (US$)	Cost community-based management (US$)
Floyd et al [277]	South Africa	1,775.70	649.30
Floyd et al [278]	Malawi	228	106
Migliori et al [285]	Italy	16,703	5,946
Moalosi et al [279]	Botswana	2,206	1,106
Nganda et al [280]	Kenya	294	120
Okello et al [281]	Uganda	419	289
Wandwalo et al [282]	Tanzania	102	75
Weis et al [286]	USA	15,670	700

1.8.2 Community-based models for the delivery of injectables

Community-based directly observed therapy for patients receiving oral short course chemotherapy for TB has a long established and successful history in Malawi and many other countries [287]. Until recently however, there were no published data on the management of patients in the community who require injections as part of their TB treatment. With the advent of MDR-TB, community based models have been developed. These models were recently summarised in a systematic review, which identified 10 publications evaluating community-based care in the

management of MDR-TB. The models used a variety of approaches, which included patients travelling daily from the community to a health facility, or a professional health care worker visiting patients in their homes [288]. Treatment outcomes in these studies were comparable to other studies which have looked at MDR-TB management, with 65% of patients successfully completing treatment.

There are a number of potential problems with the current models of community-based care for patients requiring injectables. The first model, of nurses visiting patients at home, is likely to be more cost effective than hospital-based care for health systems in the long run because of the large overhead costs of providing in-patient care. However, the organisation of daily visits by nurses to the community often requires the institution of a separate funding stream. Only one study in the review specifically reported nurses delivering injections in patients' homes. In this case, nurses were compensated $2 per day, and the mechanism used to support this was described as 'philanthropic funds' [289]. Partners in Health, a large American NGO, has established very successful community based MDR treatment programmes in Peru, Russia and Lesotho which, although run in conjunction with local NTPs, still rely heavily on PIH for support in terms of both finances and expertise [290].

The Malawi Guidelines for the community-based management of MDR-TB were adapted from the successful MDR-TB programmes in Peru and Lesotho. Personnel from the local health centre are trained to visit patients at home and deliver treatment on a daily basis. However, it is the experience of the operational programme in Malawi, which has less direct external support, that nurses often do not achieve this. Reasons have included lack of fuel, lack of N95 masks, lack of incentives (particularly for weekend visits) and being too busy at the health centre.

An alternative approach has been for patients to travel daily to a health facility in order to receive injections. A number of projects delivering MDR care have been run in this way [289, 291, 292]. However, the financial burden of daily travel to the health facility has not been fully assessed, and it is now well recognised that costs of

transport are a barrier to adherence [293]. Experience of this model of ambulatory care in Malawi for patients on retreatment has been disappointing. This has primarily been because patients frequently run out of funds and therefore miss doses due to lack of transport; but there have also been a few instances in which health care workers were reluctant to deliver injections without receiving additional financial incentives (personal communication; Dr J Mpunga, Programme Manager, Malawi NTP). As such, the community-based model of ambulatory care was abandoned and all patients are now admitted to hospital for the full 60 days of injections.

Over recent years in industrialised countries, programmes of outpatient parenteral antibiotic therapy (OPAT) have been developed and successfully instituted [294]. These programmes have employed various methods of care delivery, including patients attending a health facility daily and nurses visiting patients at home. Increasingly, family members are being trained to give parenteral medications to patients at home [295, 296]. Evidence is that these services are safe, well received by users, and highly cost effective [297]. The approach has been so successful that guidelines for OPAT services now exist in both the USA [298] and the UK [299]. Diabetic patients in poor countries are frequently prescribed insulin and successfully administer sub-cutaneous injections at home [300], however no model of carer-administered intramuscular or intravenous treatment has yet been developed in Africa.

1.9 Conclusion

This chapter has summarised the features and global epidemiology of tuberculosis, and has described TB control in Malawi. A systematic review of the literature on outcomes using the WHO Category II retreatment regimen has demonstrated low success rates across a number of settings and populations. Data which evaluate factors associated with poor outcomes specifically in patients on TB retreatment are lacking. However risks factors for TB and associations with poor outcome on TB

treatment in general such as HIV co-infection, diabetes and chronic lung disease have been outlined. The cohort study presented in chapter 3 of this thesis addresses the issue of poor outcomes on Category II retreatment regimen by examining TB factors such as microbiologically confirmed TB and drug resistance; as well as non-TB factors such as medical co-morbidity and drug toxicity.

Not only is retreatment TB associated with poor clinical outcomes, it also requires daily injectable anti-tuberculous drugs for the first 60 days of treatment, for which there is no good model of delivering care. Hospital-based care is associated with the problems of nosocomial infections; economic burdens for users and providers; and substantial social disruption for families and households. Community-based models for TB treatment are preferable but few successful programmes for delivering injections as part of TB treatment have been developed that have been entirely embedded in local systems. There is therefore a gap in the evidence for provision of care which is locally adaptable, cost effective and affordable. Increasingly in well resourced settings, family members are being trained to administer parenteral antibiotics to patients in their homes. If injectable treatment for TB is to be delivered reliably and efficiently in Africa, it must be through a model of care which is financially and operationally sustainable within existing healthcare structures. The TB-RROC trial evaluated a novel mechanism for the delivery of long term injectables in TB treatment by training guardians to administer streptomycin. Clinical, economic and qualitative evaluations of this model of care delivery are presented in chapters 4, 5, 6 and 7 of this thesis; and the following chapter 2 outlines the methodological approach taken to performing the evaluation.

2 Thesis overview

2.1 Overall objectives

Given the complexities surrounding TB retreatment outlined in chapter one, the overall goal of this thesis was to gain a better understanding of the problems faced by patients receiving TB retreatment in Malawi, and to explore areas which might be amenable to interventions which could improve care. The thesis addressed two main issues, both relating to the management of patients prescribed TB retreatment regimen.

Firstly, in order to provide a better understanding of the clinical context, factors which may be associated with poor clinical outcomes on retreatment regimen were investigated. The overall aim of this study was to answer the question: "Why are health outcomes poor in adult patients prescribed retreatment regimen for tuberculosis in Malawi?."

Second, the issues associated with prolonged hospital admission were addressed. In an attempt to alleviate the problems of in-patient management during the intensive phase of TB retreatment, a community-based model of care was developed in which guardians were trained to administer streptomycin to patients at home during the intensive phase of TB retreatment. The overall aim of the study was to evaluate whether this approach would provide a better alternative to hospital-based management.

Based on these two objectives, the project was named the "TB-Retreatment Regimen: Outcomes and Care-delivery Study" (TB-RROC Study). The next section of this thesis takes some time to provide a detailed overview of the range of approaches to evaluating complex interventions followed by a justification of the approach that was taken in evaluating the new model of community-based care. Finally there is a brief outline presented of the methods used in the TB-RROC Study.

2.2 Approach to Evaluation

2.2.1 A theoretical approach to evaluation: Realistic evaluation

Evaluating a social or public health intervention is complicated by the multiple components which need to be accounted for. Studies which are targeted at groups of people involve changing behaviours, which makes them hard to control and complicated to measure. Traditionally though, evaluation of public health interventions has involved experimental approaches such as individually or cluster randomised controlled trials. 'Realist evaluation' was a new paradigm advocated by Pawson and Tilly in the 1990s, in which they critique this experimental method and propose a new approach based on realist principles [301].

The classic experimental design involves taking two similar groups of people; measuring both groups at the beginning; applying treatment to one group and not the other; measuring changes after the treatment; and comparing changes between the groups. Any changes which occurred in the treated group but not the untreated group can be put down to the impact of the treatment. This is represented by the shorthand "OXO": Observe the system (O_1), introduce a treatment (X) to one group, observe the system again (O_2). Pawson and Tilly argue that this OXO methodology fails to produce useful information in the evaluation of social interventions for the following reasons:

1. Experiential methods subscribe to a 'successionist' view of causation. In other words, that we do not and cannot observe causal forces at work, and that causation can only be inferred from that which can be observed. Cause and effect is therefore established by observing repeated succession of one event by another ('constant conjunction'). In contrast, 'generative' theory holds that there is a real connection between events which are connected causally. Elucidating these internal mechanisms (which may be observed or unobserved), is what allows us to determine causation. This is demonstrated using the example of the prisoner who was rehabilitated. The external observable cause for this might have been a prisoner education programme. But, crucially, there

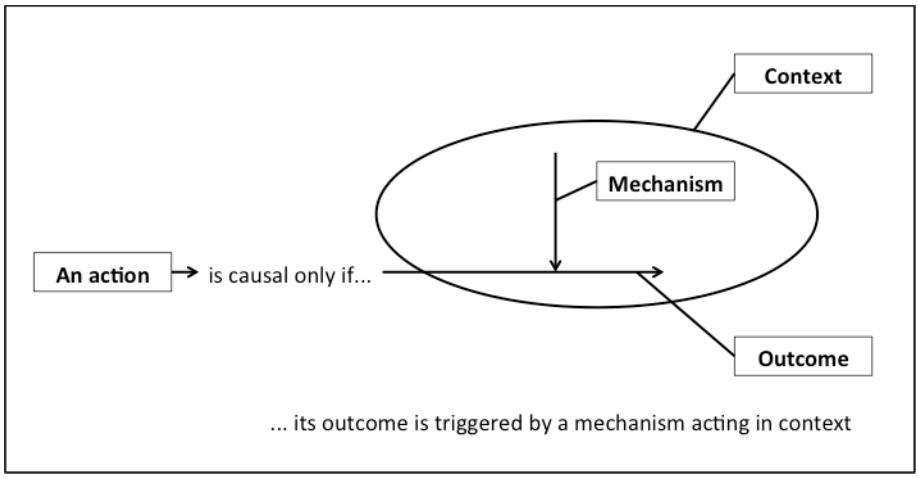
is also an internal feature that is changed – the disposition of the prisoner, which resulted in his rehabilitation. It is this internal change which allows us to make sense of the causal relationship between education programme and rehabilitation. As the aim should be to understand causal mechanisms rather than establish constant conjunction patterns, the use of the counterfactual in experimental models is misguided. Instead, investigations should be driven by the development of sound theory about which causal mechanisms may operate to produce observed outcomes.

2. Invariably experimental designs show that interventions 'work' sometimes but not all the time. This is fundamentally because social interventions involve the complex interaction of people with systems and depend on the choices people make, which vary considerably according to individual preferences, experience and circumstance. It is not the programme which 'works' but the way people respond to resources, practices and ideas that programmes introduce which influence outcome. Findings from different studies are therefore frequently inconsistent, leaving it hard for policy makers to interpret results. Evaluators should therefore not be aiming to answer the question 'does it work?', but rather to help unravel the questions of 'How does it work, for whom and in what circumstances?'

Pawson and Tilly's response to these issues is to suggest an alternative '*realist*' mode of evaluation [302]. They argue that crucial to determining what works, for who, and in what circumstances, is recognising that variations in outcome are determined by the fact that different mechanisms acting in different contexts will result in different outcomes. In other words, Context (C) + Mechanism (M) = Outcome (O). In order to understand outcomes, rather than following the OXO approach, it is necessary to design programmes which explore *theories* of which 'CMO' patterns are operating in any given intervention or programme. This is in keeping with the generative theory of causation and underpins the realist approach to evaluation (figure 9).

In order to illustrate the approach, Pawson and Tilley provide an example of the effect of a social intervention on crime rates on an estate. They identify different contexts within the estate, which combine with various social mechanisms to produce a variety of outcomes, some examples of which are summarised in table 11.

Figure 9. Generative causation - the basis for the realist experiment



Adapted from Pawson and Tilley [301]

Table 11 Examples of context, mechanism and outcome configurations

Context	+	Mechanism	=	Outcome
Area A: poor-quality housing; lack of tenant involvement in estate management	+	Improved housing and increased involvement in management create increased commitment and increased stability	=	Reduced burglary prevalence
Area B: poor-quality housing; lack of tenant involvement in estate management	+	Increased involvement in management created increased territoriality, unattractive housing maintains high turnover, retraining vulnerable families	=	Stable burglary prevalence
Area C: Tower blocks occupied mainly by the elderly, lack of tenant involvement in estate management	+	Concentration of elderly residents creates vacancies taken up by young, formerly homeless, who have little inclination for informal social control & generate an estate subculture	=	Increased burglary prevalence

Adapted from Pawson and Tilley [301]

By definition, the approach to designing an evaluation must depend on the theories underpinning it and the purpose of data collection is to confirm, falsify or refine theory. Thus, the chosen methodology for data collection must be aligned with this purpose. Realist theory traditionally rejects the RCT as a tool for assessing complex social interventions [303]. Berwick highlights their deficiencies [304], suggesting that public health programmes involve "complex, multicomponent interventions – essentially a process of social change. The effectiveness of these systems is sensitive to an array of influences: leadership, changing environments, details of implementation, organisational history, and much more. In such a complex terrain, the RCT is an impoverished way to learn." However, there have been suggestions that in fact combining realist theory with randomised trials can produce valuable insights.

Whilst agreeing that intervention research should be theory-driven, Bonnell et al disagree with Pawson and Tilley about the value of RCTs in evaluating complex interventions [305]. They argue that counterfactuals are necessary when researching social interventions "precisely because these sorts of experiments involve much more complex causality, where is it not possible to isolate the effects of one causal factor from another." They also point out that, if designed properly, 'realist RCTs' can be used to address questions of what works for whom and in which circumstances, by, for example using multi-arm studies and performing stratified sub-group analyses [306]. What is more, RCTs are able use theory-driven approaches to examine mechanisms of change by evaluating different components of an intervention as well as overall outcomes. They recommend that realist RCTs should not only focus on processes but also on the development and validation of theories of intervention which aim to explain how contexts and mechanisms interact. All of these components should employ mixed quantitative and qualitative methods in order to provide robust data.

The view that realist RCTs can provide the data required to influence policy has underpinned this work. Some of the key 'CMO' configurations which this study

aimed to examine are outlined in table 12. The theories underpinning these interactions have been reviewed in section 1.8, but are presented here again within a realist framework. In evaluating a community-based intervention for providing care during TB retreatment, the outcomes of importance were identified as falling into three broad domains: clinical, social and economic.

Table 12. Contexts, mechanisms and outcomes evaluated in the TB-RROC Study

Context	+	Mechanism	=	Outcome
				Clinical
Poorly resourced government-run health services in Malawi	+	Trained guardians learn to safely deliver streptomycin in the community	=	Clinical outcomes are as good as hospital-based care
Poorly resourced government-run health services in Malawi	+	Guardians are unable to safely administer streptomycin; sick patients unable to access care	=	Clinical outcomes are not as good as hospital-based care
High rates of default from TB treatment and HIV care	+	Control over health decisions means patients and guardians more invested in own health	=	More engagement in healthcare results in lower default rates
				Social
Patients & guardians affected by TB have strong social networks	+	Community & family able to offer support more easily as burden of travel to hospital is relieved	=	Patients & guardians maintain community relationships more easily
Families affected by TB have children who are left at home when patients are admitted	+	Patients and guardians are able to care for children when managed at home	=	Children receive better support & are able to attend school
Patients are confined to overcrowded TB wards	+	Patients and guardians can live in their own homes and continue normal activities	=	Dignity and independence are maintained
				Economic
Households suffer economic burden of hospital admission	+	Less money spent on food and transport after patient discharged from hospital	=	Reduced costs to patients & households
Patients & guardians are unable to work whilst in hospital.	+	Patients & guardians are able to continue working. Livelihoods are not disrupted.	=	Reduced lost earnings for patients and households
Overcrowded TB wards due to large numbers admitted for injections	+	Fewer patients on TB wards	=	Reduced health system costs

2.2.2 A practical approach to evaluation: MRC guidelines

In 2008, the Medical Research Council (MRC) updated their 2000 guidelines for developing and evaluating complex interventions [307]. Complex interventions are usually described as interventions which are "built up from a number of components, which may act both independently and interdependently" [308]. However, they may have other characteristics (box 1) and it is fair to say that there "is no sharp boundary between simple and complex interventions…few interventions are truly simple, but the number of components and range of effects may vary widely" [309].

Box 1. What makes an intervention complex?

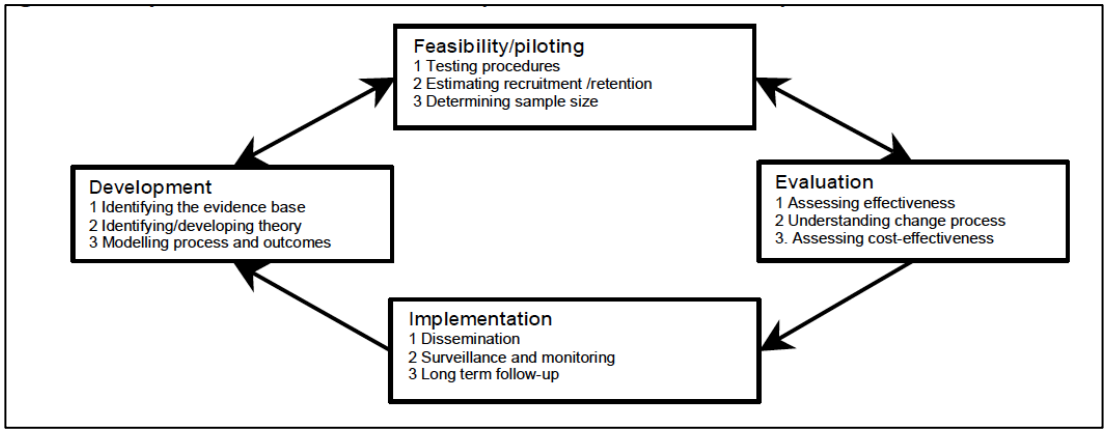
- Number of interacting components within the experimental and control elements
- Number and difficulty of behaviours required by those delivering or receiving the intervention
- Number of groups or organisational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted

From MRC guidelines for developing and evaluating complex interventions [307]

Although the TB-RROC intervention involved a single component (teaching guardians to deliver streptomycin injections), it nevertheless fulfils many of the other criteria of a complex intervention, and as such lessons can be learnt from guidelines regarding these types of interventions. For example, guardians were required to attend training and follow a series of instructions which they then had to adapt and implement in their home environment; both patients and guardians were expected to participate and work together; a number of different outcomes were assessed including clinical, economic and social; and the intervention was flexible, always tailored around the needs of the patients and guardians (e.g. the number of days of training varied considerably according to guardians availability and competency).

The basic outline of the MRC guidance is shown in figure 10 and consists of four stages. It begins with development and then piloting, before evaluating and finally implementing the intervention.

Figure 10. Key elements of the development and evaluation process



From MRC guidelines for developing and evaluating complex interventions [307]

The MRC views randomised methods as generating the strongest type of evidence, however the new guidelines recognise that "good theoretical understanding is needed of how the intervention causes change, so that weak links in the causal chain can be identified and strengthened" and identifying theory is a component of the development stage of the process. However, they have been criticised for not providing clear guidance on how to develop such theory [310]. They also state that "ensuring strict standardisation may be inappropriate: the intervention may work better if a specified degree of adaptation to local setting is allowed for" [309].

The 2008 MRC guidelines on evaluation also stress the importance of evaluating the *processes* involved in the programme, not simply the outcomes. It is important not to confuse 'process' – the actions which happen within a programme, and 'mechanism' – the explanation for why things do or don't happen within a programme. The evaluation of process is a concept which has been central to evaluation since it's early days, when Avedis Donabedian proposed that the key components of assessing quality of care were 'structure' – the attributes of the settings in which care occurs, including resources, staff and organisational

structure; 'process' – what is actually done in the giving and receiving of care, for example the waiting time for consultations, or the number of investigations performed; and 'outcome' – the effects of health care on the health status of patients and populations [311]. Once again, the guidelines have been accused of not providing enough detail on *how* to evaluate process, and further work has provided additional guidance [312].

In summary, this thesis draws on the values outlined in the realist approach to evaluation, in particular emphasising the importance of developing theory and understanding how interventions work by the examination of both context and mechanism. Although randomised experiments are shunned by purist realist evaluators, newer guidance from the MRC and others has begun to recognise the importance of many of the principles advocated by the realist camp. Thus recommendations for the conduct of RCTs now include strong reference to both theory and context. The TB-RROC study therefore begins with a cohort study which aimed to examine the clinical context of TB retreatment more closely. Published literature was reviewed in order to build theories to explain the mechanisms which are important for clinical, social and financial outcomes in the context of TB care in Malawi. The intervention of training guardians which aimed to improve social and economic outcomes of TB retreatment was then evaluated using multiple data collection methodologies to test these theories.

2.2.3 Pragmatic trials in evaluation

It is clear that the context in which a programme is implemented is a central component of the way in which it is evaluated. By imposing strict limitations on the design of a trial in order to maximise internal validity, many explanatory trials have been criticised for not providing information which is applicable to operational situations [313]. Most RCTs aim to establish efficacy, in other words, whether a treatment can work in ideal conditions. Many exclude patients who are deemed to be at high risk of non-compliance or adverse events (e.g. pregnant women, patients

with co-morbidity), and study staff are usually expected to follow strict protocols in order to make it simpler to demonstrate efficacy. As a consequence, the results of many RCTs are hard to generalise beyond such strict confines and are difficult interpret when working in standard clinical settings [314]. The objective of pragmatic trials is "to assess whether treatments work in conditions more appropriate to routine practice" [315]. The term 'pragmatic' in reference to interventions was proposed by Schwartz and Lellouch who described 'explanatory' trials as those which test a causal research hypothesis and 'pragmatic' trials as those which help users to choose between options of care [316]. There are few instances in which a trial is fully pragmatic or fully explanatory, and most lie somewhere on the pragmatic-explanatory continuum [317]. However, there are some features which characterise pragmatic trials, and these can be used to assess where on this spectrum a study lies. Where a trial lies, or should lie, on the spectrum will depend very much on the intended purpose of the study (decision-making v explanation).

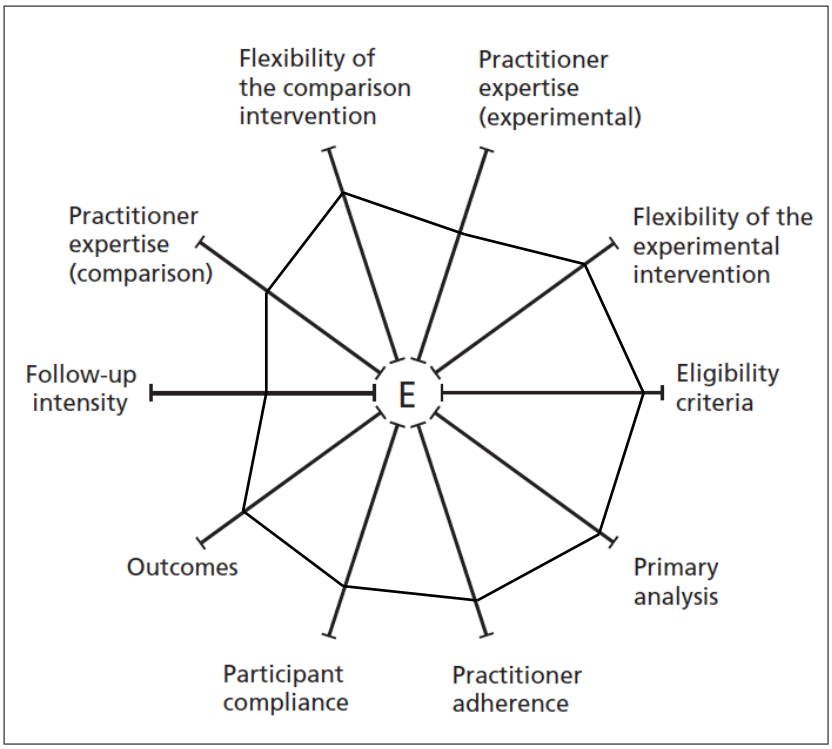
In 2009, Thorpe et al published "A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers" [318]. The aim of the tool is to help researchers examine the extent to which their trial design aligns with their stated purpose and therefore adjust the design to be more in line with the aims of the project. It can also be used by policy makers and implementers to assess how generalisable the results of the study are and therefore how applicable they may be to a particular setting. The tool consists of 10 domains which determine the extent to which an intervention is pragmatic or explanatory. These domains are presented in a wheel with the explanatory end of the spectrum at the centre (E).

There are a number of features of the TB-RROC study which were specifically designed in order to make the trial as far towards the pragmatic end of the continuum as possible (figure 11):

1. Eligibility criteria

There were no strict clinical criteria for entry into the study. No blood tests were necessary prior to enrolment, and the only clinical requirement was for a clinician to declare the patient fit for discharge. This was based on national guidelines and our own personal experiences of the health system in Malawi in which blood tests are not routinely performed on patients with TB (even those receiving retreatment) unless there is a specific clinical indication for doing so. Pregnant women were excluded because streptomycin is contraindicated in pregnancy, and they should therefore not be receiving standard Category II regimen. Likewise, although patients with identified rifampicin resistance or MDR-TB, patients without a guardian, and patients not well enough for discharge were all excluded, these exclusion criteria would also always apply in routine practice, as it would never be appropriate for these people to receive community-based management for TB retreatment.

Figure 11. TB-RROC trial PRECIS diagram



2. Flexibility of the experimental intervention

The intervention was designed to accommodate the needs of the study participants. For example, patients were able to nominate their guardian and training and follow up were arranged for the convenience of the participants. Although provided with some basic training tools, the style and content of the training sessions were essentially left to the discretion of the study nurses.

3. Practitioner expertise (experimental)

During consultation with the Malawi NTP in the initial development stage it was established that should the intervention be adopted as policy, routine follow up visits would be carried out by health surveillance assistants. Therefore, follow up visits in the trial were conducted by fieldworkers with a level of training and experience comparable to that of HSAs. Both nurses employed full time on the study were highly experienced research nurses, however at both sites the sister in charge of the TB ward (employed by Ministry of Health) was also a full member of the study team, attending all training, receiving a monthly stipend, and running the study when the research nurse was unavailable. It was anticipated that nurses at this level would deliver the intervention in routine settings were it to be successful.

4. Flexibility of comparison intervention

Participants in the comparison group received standard of care, delivered by the medical and nursing staff on the TB wards at the two sites. The addition of a study doctor to each of the wards during the study period may have resulted in an enhanced level of care for patients in hospital. However the doctors were members of the medical team delivering care to all patients on the TB wards, regardless of their participation in the TB-RROC study, and were therefore simply part of the standard care for all patients with TB during that period, and functioned in the same way as other doctors at the same level function on the wards.

5. Practitioner expertise (comparison)

Participants in the comparison arm received routine care from staff on the wards, with little additional input from the study team.

6. Follow-up intensity

Despite concerns from some academic colleagues that no Therapeutic Drug Monitoring (TDM) was being performed in order to assess adherence, TDM was not carried out in the study. Performing TDM on patients in the community would alter the applicability of the results for two reasons: i) a nurse would have to perform the follow up visits (see point 3), and ii) having blood tests would likely alter participants' behaviour, making the results difficult to interpret in a setting where TDM would not routinely be done. The follow up schedule of visits at 1, 3, 5 and 7 weeks post discharge was again derived from discussions with collaborators at the NTP and based on what they considered would be practical for a district TB office to implement. All follow up visits were performed by fieldworkers visiting study participants at home, but it became apparent that this may not always be possible under routine conditions. In practice, it may be that patients would be asked to attend the health facility for some follow up visits, which would constitute slightly less intense follow up.

7. Outcome measure

The outcome measure of the study was an outcome which is measured routinely in TB reporting. If a patient was still alive and attending the hospital for treatment at the end of the intervention period, it was considered a treatment success. Whilst microbiological tests formed a component of the secondary outcomes, this was not the primary outcome of the study as sputum culture is not routinely performed after 2 months of TB retreatment in Malawi.

8. Participant compliance

The importance of adherence in TB treatment cannot be overlooked in any TB intervention. Adherence to treatment was closely monitored in both control and intervention arms, but this is entirely in line with operational practice.

9. Practitioner adherence to study protocol

Study staff were expected to follow a basic set of guidelines for recruitment, training of guardians, follow up of study participants, reporting and management of

adverse events. However they had autonomy in deciding, along with study participants, exactly how training and follow up visits were organised.

10. Primary analysis

The primary analysis was intention to treat, in line with the principle that the aim of the study should not be to establish efficacy under ideal conditions, but rather to assess the effectiveness of the intervention in practice.

Reporting of this study followed a published extension to the CONSORT statement, specifically for reporting pragmatic trials. This extension was published in order to help researchers present data in a standardised format to aid the interpretation and therefore use of pragmatic trails in decisions about health care [319].

2.2.4 Applied health research and evidence for decision-making

Evaluations of public health interventions are only valuable if they are used by decision-makers to improve the health of populations, and research which is inaccessible and irrelevant to those who can implement change rarely has impact [320, 321]. Rather than developing new health technologies, applied health research aims to maximise the impact of health technologies on populations by enhancing the health systems through which they are implemented and improving their delivery to populations who are most in need. A number of terms are used to describe this type of research, but this summary will focus on the definitions proposed by Remme et al who propose three research domains: 'Operational', 'Implementation' and 'Health System' (table 13) [322].

Table 13. Defining research to improve health systems

Research Domain	Primary Characteristic			Example
	Focus of research	**Users of research**	**Utility of outputs**	
Operational	Operational issues of specific health programmes	Healthcare providers, programme managers	Local	Which of the current ART payment strategies in use in Nairobi should be retained in the new integrated programme?
Implementation	Implementation strategies for specific products or services	Programme managers, R&D managers	Local/broad	How to deliver ivermectin for onchocerciasis control and ensure high treatment coverage in isolated rural communities?
Health system	Issues affecting all or some of the building blocks of a health system	Health system managers, policy makers	Broad	To what extent do health services reach the poor? How can this be improved?

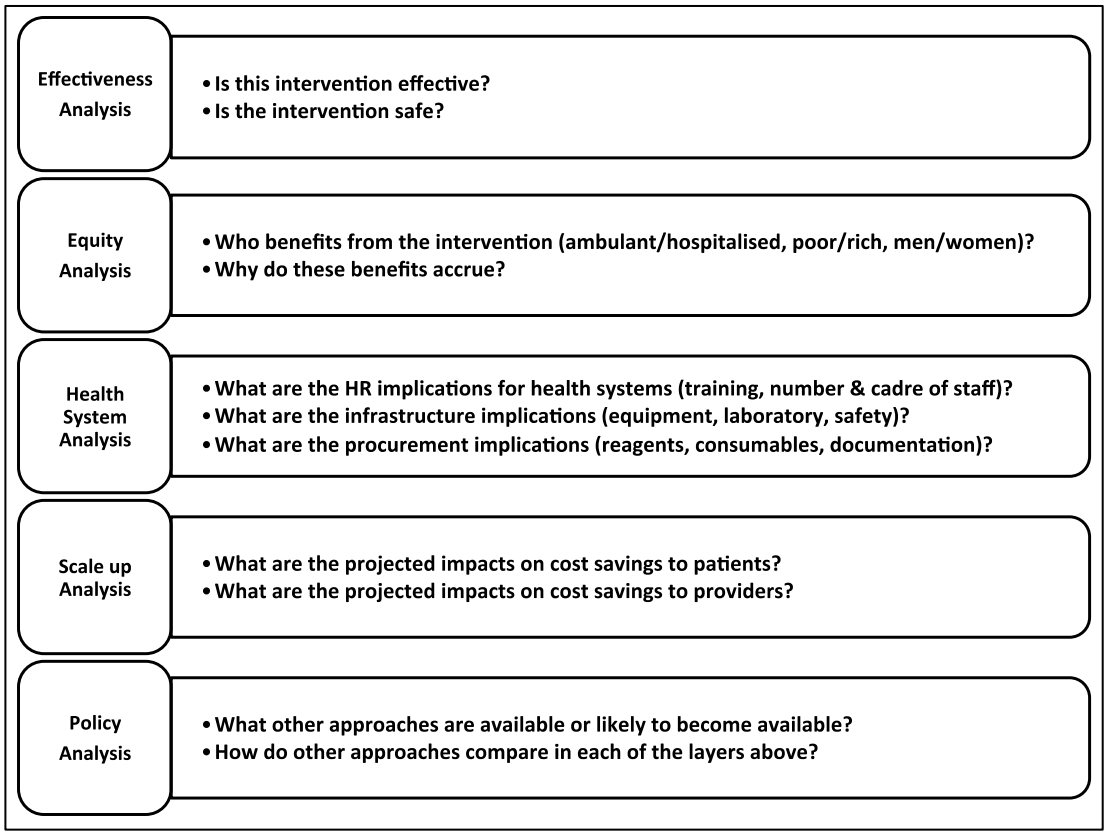
Adapted from Remme et al [322]

The utility of research outputs refers to how amenable the research is to adaptation and use in other contexts. For example, operational research is targeted at finding specific solutions for local healthcare problems and is focussed entirely on the context of that particular situation. It therefore has limited applicability beyond the setting in which it is conducted (although if the context is well evaluated and described, it may still provide important lessons for other settings). On the other end of the spectrum, health system research addresses much broader questions which are not disease specific but rather pertain to issues which have repercussions for the health system as a whole. The WHO/UNICEF/World Bank Special Programme for Research and Training in Tropical Diseases defines implementation research as that which "addresses implementation bottlenecks, identifies optimal approaches for a particular setting, and promotes the uptake of research findings," once again stressing the importance of understanding the specific context in which the implementation is carried out [323]. Implementation research is intervention specific but, unlike operational research, it aims to provide information which is applicable beyond the local area in which it is conducted. The TB-RROC study evaluates a specific new model of care delivery relevant to the local contexts in Lilongwe and Blantyre, but it also provides information applicable to other settings both nationally and potentially further afield, particularly in settings where it is

standard to admit patients requiring injectables for retreatment or MDR-TB [324]. According to the definitions discussed, the TB-RROC study is therefore best categorised as 'implementation research'.

The driving force behind any applied health research is its potential for translation into practice [325]. In order for this process to be successful, it is important that research is designed appropriately. In order to help produce strong evidence to support decision-making in tuberculosis programmes, Mann et al developed the 'Impact Assessment Framework' [326]. The IAF proposes five layers of evaluation which together will provide a comprehensive assessment of the potential impact of an intervention (figure 12).

Figure 12. Impact Assessment Framework



Adapted from Mann et al [326]

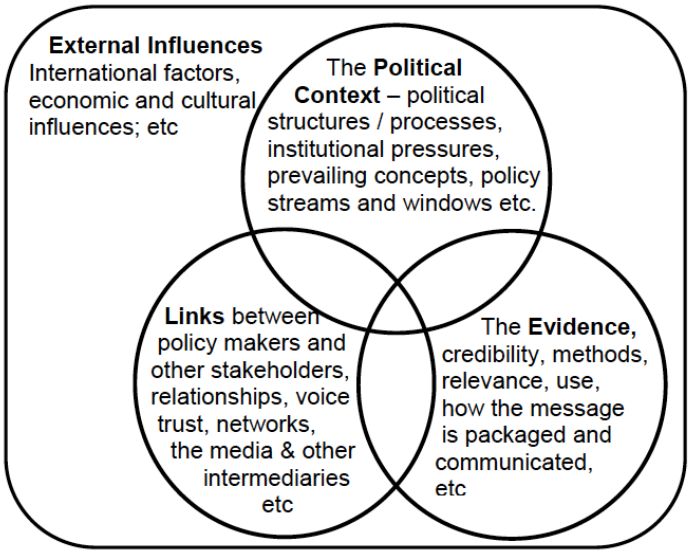
The TB-RROC study incorporated layers of the IAF which were practical given the available resources and time. Effectiveness was assessed primarily by conducting an RCT, although some aspects of safety were also addressed in a qualitative

evaluation. In terms of equity, the effects of the intervention on the poor were of particular interest and this was examined by analysing user costs for different quartiles of wealth, as well as addressing issues of poverty in the qualitative analysis. The potential effects of scale up on costs to patients and providers were evaluated in a full economic analysis which estimated both user and health system costs.

It is recognised by the developers of the IAF that "evidence alone is often not the only driver of policy change". In addition to evidence, other important factors include developing partnerships for capacity building; and collaborating with policy players in order to understand political context and external influences [325]. In recent years there has been a move away from viewing the interaction between research and policy as a one way linear process, requiring transfer of knowledge from researcher to policy maker [327]. The assumption that there is a clear divide between researchers and policy makers has also been challenged [328]. Instead, the whole relationship is now seen as a much more complex and dynamic process, and there has been a surge of literature about the research-policy interface [329-333]. A key piece of work which sets out set out a broad framework for the practical translation of research into policy is The RAPID (Research and Policy in Development) framework developed by The Overseas Development Institute (ODI).

The ODI points out that "better utilisation of research and evidence in development policy and practice can help save lives, reduce poverty and improve quality of life" [334]. The RAPID framework identifies a range of inter-related factors which can be used to determine the likelihood of evidence being adopted by decision-makers (figure 13). Four broad issues in the research-policy interface are outlined: the political context (which shapes the relationship between research and policy); the evidence (in particular the quality, relevance and communication of evidence); links (with communities, networks and intermediaries which are crucial in affecting policy change); and finally external influences (such as donors and funders who invariably have influence on policy).

Figure 13. The RAPID framework



From ODI [335]

Although the TB-RROC project was a relatively small scale evaluation forming the basis of a PhD fellowship, attempts were still made at all stages to incorporate best practice recommendations for generating evidence and working with decision makers to optimise the potential for impact. As such, the Malawi NTP was involved in the development of the project from the pre-protocol stages. An initial meeting was held in April 2012 in which the basic components of the project were discussed and agreed upon. The meeting was used to ensure that the intervention was designed to be as representative of the operational situation as possible, and that relevant evidence required for decision-making by the NTP was generated. The Lilongwe site was managed by the programme's Care and Treatment officer who was seconded by the NTP to be the co-PI at Bwaila hospital. This ensured not only theoretical but also practical involvement of the NTP throughout the project, and helped to form a strong link between the project and the NTP. The views of other stakeholders were also incorporated into the project by convening a Community Advisory Board which met throughout the study (figure 14); and by involving Ministry of Health nurses working on the TB wards as part of the study teams at both sites. Finally, at the conclusion of the study, a feedback session was held with study participants in which the results of the project were presented and discussed

(figure 15). Evidence was presented and discussed at regular intervals with both the NTP and the CAB, and as the final results of the project are being generated, discussions with the NTP are on-going. The terms of reference for the CAB are outlined in appendix 1.

Figure 14. Community Advisory Board

Figure 15. Participant feedback

It was clear that in order to answer a broad range of questions concerning issues relating to effectiveness, safety, context, equity and costs, it would be necessary to use a number of different research tools to evaluate the TB-RROC intervention. It is

well recognised that applied health research is often strengthened by the use of multiple methodological approaches, in order to obtain rich data from different perspectives which can add value individually or be used in conjunction to 'triangulate' findings [305, 322, 336]. In addition to quantitative methods such as RCTs, 'mixed methods' studies use qualitative methods to provide data which cannot easily be captured by quantitate methods, such as information about context, experiences, beliefs and attitudes [337, 338]. Applied health research studies are also increasingly including economic evaluations in order to assess the financial impact of health interventions for both service users and policy makers [339].

2.3 Summary of TB-RROC Study methods

2.3.1 Investigating reasons for poor clinical outcomes on TB retreatment

In order to examine factors associated with poor clinical outcome on TB retreatment regimen, a prospective cohort study was conducted. Patients starting TB retreatment were recruited from QECH. The primary outcome of the study was successful completion of the 8 month course of treatment. The exposure of interest was microbiological confirmation of TB by sputum smear, culture or GXP. Other variables which it was hypothesised would be associated with TB treatment outcome were co-morbid medical conditions (such as chronic lung disease and HIV), drug toxicities, burden of TB infection and drug resistance. Patients were reviewed at baseline, after 2 months of treatment and at completion of 8 months of treatment.

2.3.2 Evaluation of a community-based model of care during TB retreatment

A mixed methods approach was taken to the evaluation of a community-based intervention which involved training guardians to deliver streptomycin in patients' homes. A pragmatic, individually randomised trial assessed effectiveness by comparing clinical outcomes at 2 months in patients randomised to community-based management to clinical outcomes at 2 months in patients randomised to

receive hospital-based management. The trial was powered to detect non-inferiority in the intervention arm. Patients were recruited from QECH in Blantyre and Bwaila Hospital in Lilongwe. The importance of examining how the intervention might work for different groups of users was recognised. However, the time available did not allow for recruitment of a large enough cohort into the RCT which would enable formal statistical sub-groups analysis. Further evaluation consisted of a formal qualitative study which aimed to describe the experiences of patients and their guardians during the intensive phase of TB retreatment (context), and how these experiences were affected by community-based care (mechanisms of the intervention). The qualitative evaluation was used to gather detailed information about the experiences of a wide variety of study participants and key informants. Finally, an economic evaluation was performed in order to a) provide cost data which would be relevant to decision-makers, b) explore the consequences of community and hospital-based care during TB retreatment on costs to households, and c) describe the financial consequences of undergoing TB retreatment in different groups, particularly the poor.

In these ways, the multi-method evaluation provided a comprehensive understanding of the clinical, social and financial impacts of the intervention with the aim of affecting a change which worked for individuals, families and communities. Relevant data alongside engagement with decision makers throughout all stages of the project aimed to ensure that the study was conducted in a way which was relevant to policy and also had local context at the forefront. By addressing the challenge of providing long term injectables to patients with tuberculosis in the community using an entirely new approach in resource limited settings, the study addressed a crucial gap in research and practice.

2.4 Study sites and population

The TB-RROC Study was conducted across two sites. Queen Elizabeth Central Hospital (QECH) in Blantyre is the largest hospital in Malawi, and admits over 10,000 adult patients a year. It serves as the tertiary referral unit for the southern

region of Malawi and is attached to the country's only medical school. TB care in Blantyre is managed by the TB office based on the TB ward at QECH, and also by the District TB Officer, based at the local District Health Office located close to the hospital. Since 2011, a process of decentralisation has meant that there are now 11 TB registration centres based at primary health centres around Blantyre. All patients requiring retreatment regimen are referred to QECH for hospital admission in order to receive streptomycin injections delivered by nurses on the ward. The organisation of TB care in Lilongwe follows a slightly different model. Bwaila Hospital is run by the Lilongwe District Health Office and there is no emergency adult care facility. Patients are admitted to the TB ward at Bwaila via a number of pathways. Those who present acutely to Kamuzu Central Hospital in Lilongwe (the tertiary hospital serving the central region) are transferred to Bwaila Hospital for further TB care once they have been clinically stabilised. Patients diagnosed with recurrent TB from any of the health centres around Lilongwe or at the integrated TB-HIV clinic based on site are referred directly to the ward at Bwaila for admission. In 2010, there were approximately 300 registrations in Blantyre and 350 registrations in Lilongwe for TB retreatment regimen (data from Malawi NTP).

At both centres, a study office was established on the TB ward. At QECH, this was a room off the main corridor of the ward, next to the TB office. At Bwaila, this was an office adjacent to the nurses' office which was positioned between the two free-standing (male and female) TB wards. The study teams were based permanently at these offices and were therefore well integrated into the day to day activities of the wards.

The TB-RROC Trial was conducted at both sites. The cohort study recruited patients only from QECH as this was the site with access to resources such as spirometry, audiology and CT scanning.

2.5 Data management

Data were managed at the Malawi Liverpool Wellcome Centre and followed MLW standard operating procedures in relation to data handling and consent. All data collected, stored and shared were GCP compliant [340].

Patients recruited to the study were assigned a study number at the time of recruitment, and from this point all data were anonymised. The study team collected data on paper Case Record Forms (CRFs). Original paper records including CRFs and consent forms were stored securely in locked filing cabinets in the research offices.

Data were captured to electronic form using Teleform® scanning software (Cardiff Software Inc). Data from the Blantyre site was scanned directly using Teleform® scanning equipment. Data from the Lilongwe site were scanned to electronic file and then transported to Blantyre for transfer into the Teleform® system. Data were verified at regular intervals and discrepancies resolved. Data were then exported automatically to a secured database in Microsoft Access. Data files were exported to STATA 12 for analysis. Access to the study database was password protected, and the number of people with access to the database was limited to the principal investigator, study supervisors and co-investigators at the NTP.

2.6 Ethical considerations

Written informed consent

Written (or witnessed in the case of participants who were illiterate) informed consent was obtained from both patients and guardians. Consent was obtained separately for participation in the trial, the cohort study, and the qualitative study. Each participant should have the right to decline entry into the study without influence. Therefore patients and guardians were each asked separately to provide informed consent for participation in the trial. They were both given the chance to ask questions and to discuss between themselves prior to being asked to provide

consent. It was made clear that participation in any part of the study was voluntary and that consent to participate could be withdrawn at any time without affecting the care of the patient.

Ensuring privacy and confidentiality for participants

All consultations involving study participants aimed to maintain privacy and were performed in a private room wherever possible. Consultations during the trial and cohort studies took place in the study offices based on each ward. For the qualitative evaluation, interviews were conduced in a private room away from the ward. Patients recruited to the study were assigned a study number at the time of recruitment, and from this point data were anonymised.

Ethics Committees & Trial Registration

The studies were approved by the Institutional Review Boards at College of Medicine, Blantyre, Malawi (COMREC) and Liverpool School of Tropical Medicine, Liverpool, UK. The Trial was registered under the identifier ISRCTN05815615.

2.7 Conclusion

This chapter has reviewed approaches to evaluation, with a particular focus on the theory of 'realist evaluation' as described by Pawson and Tilley. The ideas underpinning the TB-RROC evaluation have been presented in the context of realist evaluation and the methodology described in line with the MRC guidelines for the evaluation of complex interventions. The TB-RROC evaluation aimed to provide data which would be of use for decision makers and hence the trial was designed pragmatically, and evaluated using mixed methods to holistically assess the new model of care delivery.

In addition to providing an overview of the methods used in evaluation of the TB-RROC trial, this chapter has briefly described the methods used in a cohort study which investigated clinical outcomes on TB retreatment. The thesis now goes on to describe each of these studies in detail.

3 The TB-RROC Cohort Study

3.1 Introduction

It is well recognised that clinical outcomes on Category II retreatment regimen for TB are poor, and further data to support this has been presented in a systematic review of the literature in chapter 1 of this thesis. Reasons for the low rates of successful treatment completion are not well established, but may include drug resistance, poor adherence, drug toxicities and medical co-morbidities. This chapter describes a prospective cohort study which was performed in Blantyre in order to examine in detail factors which may be associated with poor treatment outcome on Category II regimen.

3.2 Aims and objectives

The overall aim of this study was to answer the research question:

"Why are health outcomes poor in adult patients prescribed retreatment regimen for tuberculosis in Malawi?"

Specific objectives were:

1. To determine the prevalence of smear, culture or GeneXpert (GXP) confirmed TB in patients receiving TB retreatment regimen, and to compare health outcomes in patients with confirmed TB to those without confirmed TB.
2. To describe the following features in patients on TB retreatment regimen and determine if any are associated with poor health outcome:
    - Burden of TB infection (by bacillary load)
    - Resistance to drugs used in the retreatment regimen
    - Infectious and non-infectious co-morbidities
    - Adverse events associated with anti-tuberculous drugs

It was believed that the presence of microbiologically confirmed TB would be the explanatory variable most predictive of clinical outcome [341, 342]. It was for this reason that the primary objective of the study (and therefore basis of the sample size calculation) was to determine whether there was an association between microbiologically confirmed TB and clinical outcome. Data about other clinical features in patients recruited to the study were also collected in order to evaluate whether there were additional explanatory variables that were associated with poor health outcome.

3.3 Methods

3.3.1 Study design

This was a prospective cohort study, which recruited consecutive patients starting TB retreatment regimen at QECH. Those recruited had a number of clinical assessments during the course of their treatment, which aimed to identify factors that may be associated with clinical outcome. Patients were assessed at three time points: at the start of TB treatment, after 2 months of treatment, and at completion of treatment after 8 months (table 14).

Table 14. Data collection schedule for TB-RROC cohort study

	Month 0 (Enrolment)	Month 2 (End of streptomycin)	Month 8 (Completion of treatment)
Demographics			
Medical history			
Clinical examination			
Smoking history			
Alcohol history			
Audiological assessment			
Blood tests			
Creatinine, ALT, Bilirubin			
HbA1c			
HIV test +/- CD4 & VL			
Urine dipstick			
Sputum examination			
AAFB smear			
GXP			
MGIT culture			
DST			
Radiological assessment			
Chest X-ray			
CT scan thorax			
Lung function testing			
Audiological assessment			

3.3.2 Outcome measures

The primary outcome measure was:

"*Successful 8-monthTB treatment outcome".*

The definition of 'successful 8-month treatment outcome' was based on the WHO definition of successful TB outcome, which includes those who are cured and those who complete treatment but do not fulfil the definition of cure (table 3) [66]. Unsuccessful outcome therefore comprised those who died, those who defaulted treatment and those who were transferred out or whose treatment outcome was unknown.

3.3.3 Eligibility

Inclusion criteria

- Adults ≥ 16 years of age starting TB retreatment regimen
- Patients able to give informed consent

Exclusion criteria

- Patients identified as having MDR-TB on phenotypic drug sensitivity testing, or being treated for MDR-TB on the basis of Rifampicin resistance detected using GXP (these patients were referred to the NTP MDR treatment programme)
- Pregnant women
- Patients unable to give informed consent

Patients were only recruited from QECH. The eligibility criteria for enrolment into the TB-RROC cohort study overlapped significantly with those for enrolment into the TB-RROC trial. In fact the criteria for entry to the cohort study and the trial were essentially the same, with the exception of two points. Firstly, some patients did not come to the attention of the study team on the day they started TB treatment, for example if they bypassed the TB ward by being admitted to the intensive care or high dependency unit. As clinical assessments were required at baseline for the cohort study, patients who were screened having completed 10 or more days of TB treatment were excluded from the cohort study, whereas these patients could still be enrolled into the trial. Secondly, not having a guardian willing and able to participate in the study was not an exclusion criterion for enrolment into the cohort study. Those patients admitted to hospital with TB who do not have a guardian are likely to be a different subset of the population to those who do; for example they may be more likely to be from a lower socioeconomic background. Therefore to have excluded those patients with no guardian from the cohort study may have resulted in recruitment bias.

3.3.4 Laboratory procedures

All laboratory tests were performed at the MLW research laboratory or the MLW/COM TB laboratory in compliance with Good Clinical Laboratory Practice. The results of any tests performed in real time were made available to the clinicians caring for patients in order to aid decision-making and improve clinical care.

Biochemical & haematological testing

Serum creatinine, ALT and bilirubin levels were measured in real time using the Beckman Coulter Synchron CX® 5 PRO Clinical System. Creatinine clearance was estimated using the Cockcroft-Gault Equation:

CrCl = ((140-Age) x (Weight in kg) x constant) / Serum creatinine in µmol/L

** Constant = 1.23 for men; 1.04 for women*

Renal function was measured at baseline and after completing 2-months of streptomycin. There is no accepted classification for renal injury occurring over this period of time, therefore the RIFLE classification of acute kidney injury was adapted for use in the study [343]. It was felt that this was the most appropriate classification on which to base the definition of kidney injury, because it takes into account both serum creatinine and CrCl. As a large proportion of patients in this cohort were likely to have low or very low body weight, the addition of CrCl should be more representative of renal function than serum creatinine alone. Kidney injury was therefore defined as an increase in serum creatinine of 1.5 fold, or a reduction in CrCl by ≥ 25% from baseline. Renal impairment at baseline was defined as Creatinine >115µmol/L or CrCl <90 mL/min. Urine analysis was performed using Mission® Urinalysis Reagent Strips (ACON Laboratories), as per manufacturers instructions.

Drug induced liver injury was diagnosed if the ALT increased to >200 IU/L; there was a rise in bilirubin to >40 µmol/L; or a patient became clinically jaundiced [344-346].

Full blood count was performed in real time using the Beckman Coulter HmX® haematology analyser. Anaemia was defined as Hb <8g/dL [347]. Samples for HbA1c testing were batched and performed periodically using the AU480 Beckman Coulter® analyser. A diagnosis of diabetes was made if a patient had an HbA1c level of ≥6.5% [348].

Assessment of HIV related parameters

In patients found to be HIV positive using the standard testing protocol in Malawi (serial testing using Determine 1/2™, Alere, Waltham, USA and Uni-Gold™ Recombigen® HIV, Trinity Biotech, Bray, Ireland), CD4 count was performed using the CyFlow® Counter (Sysmex Partec GmbH, Gorlitz, Germany). In line with Malawi national guidelines, HIV viral load was performed at the QECH laboratory using the Abbott m2000 RealTime System for the detection of HIV-1 RNA (Illinois, USA) in all patients who had been on ART for longer than one year. ART failure was diagnosed based on a viral load of >5000 copies/ml, and patients who met this criteria were referred to their nearest ART clinic for initiation of second-line ART.

TB laboratory procedures

Sputum samples were decontaminated with 3% sodium hydroxide, mixed and left to stand for 15 minutes, vortexing twice at 5-minute intervals. The action of sodium hydroxide was neutralized by adding sterile phosphate buffer, following which the sample was mixed and then centrifuged at 3700rpm for 20 minutes. The supernatant was discarded; the pellet re-suspended in PBS, and a drop of sediment was placed on a slide. Once dry, slides were fixed and then stained with Auramine O; decolorized with 0.5% acid-alcohol; counterstained with Acridine Orange or Potassium Permanganate; and examined for bacilli using florescence microscopy. All positive smears were confirmed by Zeihl Neelsen staining. 0.5ml of concentrated sputum was added to a mycobacterial growth indicator tube containing 0.8ml of MGIT PANTA and OADC; and incubated using the BACTEC™ MGIT™ 960 Mycobacterial Detection System (Becton, Dickinson and Company, New Jersey,

USA) for up to 44 days. All positive samples were confirmed by ZN staining. The presence of *M. tuberculosis* was distinguished from Mycobacteria Other Than TB (MOTT) by examining for the presence of cording; testing using SD BIOLINE TB Ag MPT64 Rapid antigen test for *M. tuberculosis* (Standard Diagnostics Inc., Republic of Korea); and incubating samples on LJ slopes at 45^{o}c, 37^{o}c and 25^{o}c as well as PNB at 37^{o}c for 3 weeks. Xpert®MTB/RIF assay (Cepheid Sunnyvale, USA) was performed on raw sputum samples according to manufacturers instructions. Indeterminate results were repeated on a fresh sputum sample.

Phenotypic drug susceptibility testing was performed at the University of North Carolina research laboratory in Lilongwe using the BACTEC MGIT ® AST SIRE kit, according to their standard operating procedures. Briefly, each of the four antibiotics streptomycin, isoniazid, rifampicin and ethambutol were suspended in a MGIT tube. Organism suspension was added to each antibiotic tube as well as a growth control tube and the tubes were incubated at 35-37^{o}c. If the drug-containing tube did not fluoresce within two days of onset of fluorescence in the growth control tube, the MGIT result was interpreted as susceptible. If the drug-containing tube fluoresced on or within two days of the onset of fluorescence of the growth control tube, the result was interpreted as resistance to that drug.

3.3.5 Radiological procedures

Chest radiographs were performed at the start of TB treatment. CT thorax was performed on the SOMATON Sensation 16 scanner (Siemens) using the pre-programmed Lung Low Dose protocol as per manufactures instructions. DICOM images were transferred to a password protected electronic storage device and read using OsiriX HD software. It was planned that CT scans of the thorax would be performed on a subgroup of 100 patients after 2 months of treatment. This time point was chosen because the primary purpose of doing CT thorax was to identify patients with chronic lung disease, therefore obtaining images 2 months after the initial acute event would provide most relevant information. Chest radiographs were used in the reporting of acute lung pathology because CT scan is not always

reliably available in Blantyre, and it could not be guaranteed that all patients would have access to CT during the acute phase of their illness.

Two qualified radiologists (EJ and SG) independently reviewed and reported all chest x-ray and CT thorax images. They then used a consensus approach to decide on an agreed interpretation of each radiograph and CT series. Primary analysis was performed on the consensus interpretation of the images. The purpose of this study was not to test the sensitivity of a radiological technique but rather to provide an accurate description of respiratory pathology found on imaging. As such, radiologists had access to basic clinical information (age, sex, HIV status, duration of illness, sputum smear status, smoking history) in order to aid interpretation of the films. All reports were recorded on standardised reporting proformae (appendix 2). Initially, detailed descriptions of the images were recorded using a classification developed from guidelines for the reporting of Thoracic Imaging published by the Fleischner Society [349]. Based on these purely descriptive findings, images were further reported according to pre-defined diagnostic categories.

3.3.6 Audiological procedures

Trained audiologists from the Department of ENT at QECH performed audiological assessments on patients at baseline, 2 months and 8 months. A brief history of symptoms that may have indicated possible ototoxicity was ascertained. Following this, otoscopy was performed to rule out common causes of impaired hearing resulting from abnormality in the auditory canal or tympanic membrane such as wax in the canal or tympanic perforation. Patients in whom pathology was identified on otoscopy were referred to the ENT department for further management.

Transiently Evoked Otoacoustic Emissions (TEOAEs) were tested using the Sentiero hand held device (PATH Medical Solutions, Guymark, UK) and assessed in each ear at frequencies between 1000 and 4000 kHz. Results were graded as ‘valid response’ (indicating normal hearing) or ‘no valid response’ (indicating impaired hearing).

Pure Tone Audiometry (PTA) was performed in a quiet room using the KUDUwave 5000 audiometer (eMoyoDotnet (Pty) Ltd, Randburg, South Africa). PTA thresholds were obtained at frequencies between 250 and 1600 kHz. In line with guidelines published by the American Speech-Language-Hearing Association [350, 351] significant change in behavioural hearing sensitivity was defined as:

- ≥ 20 dB change from baseline at any one test frequency; or
- ≥ 10 dB change from baseline at any two consecutive frequencies.

In order to improve specificity for ototoxicity, this definition was further refined to include only those with change in hearing at high frequency (>8000 kHz). Vestibular assessment was performed in those patients who reported a history of imbalance or dizziness. Vestibular assessment included:

- *Romberg's test*

  The patient is asked to stand with their feet together and their arms folded. They are then asked to close their eyes. Balance loss or increased sway (side to side and/or back and forth movement of the whole body) indicates bilateral vestibular functional loss.
- *Head thrust test*

  The patient is asked to look straight ahead. The examiner moves the head slowly from side to side. The head is then moved quickly to one side. The development of nystagmus indicates vestibular pathology.
- *Clinical test of sensory integration of balance (CTSIB)*

  The patient is asked to sand bare foot on a firm surface. They are asked to fix their eyes on a point ahead, and then to close their eyes. The procedure is repeated with the patient standing on a mattress or sponge. A patient with bilateral vestibular pathology falls.

3.3.7 Lung function testing

Spirometry was performed on patients at 2 and 8 months. Baseline lung function was not assessed for two reasons. Firstly, spirometry performed during the acute

phase of a respiratory illness is unlikely to be representative of a patient's true respiratory capacity. Secondly, the risk of TB transmission posed to operators was likely to be significantly reduced after patients had been on TB treatment for 2 months.

Spirometry was performed using the EasyOne^{TM} spirometer (ndd Medical Technologies, MA, USA), according to manufacturers instructions. All operators attended training run by Spirometry Training Services Africa CC. Machines were calibrated using a 3L calibration syringe before each session. Participants were actively encouraged during the procedure to exhale maximally, and for at least 6 seconds. For each patient, it was attempted to obtain 3 reproducible, technically acceptable readings. Comparison to predicted levels used NHANES III reference ranges. The investigator interpreted all spirographs, and a second reader reviewed 20% of all tests as a quality control measure.

The following definitions were used to interpret lung function [352]:

Table 15. Interpretation of pulmonary function tests

Classification	Spirometry findings	
Normal	FEV1/FVC ≥ 70% FVC ≥ 80% predicted FEV1 ≥80% predicted	
Obstructive	FEV1/FVC <70%	
Further classified as:	Mild:	FEV1 ≥80% of predicted
	Moderate:	FEV1 <80%, ≥50% predicted
	Severe:	FEV1 <50%, ≥30% predicted
	Very severe:	FEV1 <30% predicted
Restrictive	FEV1/FVC ≥70% FEV1 <80% predicted	

3.3.8 Sample size

The sample size calculation for this study was based on the primary outcome variable and that which was believed to be most associated with successful

treatment outcome - confirmation of TB by smear, culture or GXP. It was estimated that approximately 50% of all patients on retreatment regimen would be culture positive. This was based on the assumptions that:

1. 58% of patients with pulmonary TB would be culture positive (unpublished data, Prof E.L. Corbett).
2. No patients with EPTB would be culture positive.

It was also estimated that approximately 85% of patients with culture positive TB would have a successful end of treatment outcome, and that approximately 65% of patients with culture negative TB would have a successful treatment outcome. Using openepi software (http://www.openepi.com/) it was calculated that 158 patients were therefore needed in order to detect this difference with a power of 80% at a significance level of 5%.

3.3.9 Statistical Methods

Primary analysis

Univariate analysis of associations with the primary outcome of 8-month treatment success was performed using logistic regression and presented as unadjusted odds ratios with 95% confidence intervals. Multivariate analysis was performed using a logistic regression model to produce adjusted odds ratios with 95% confidence intervals. The model was adjusted for the predefined variables: age group, gender, HIV status and variables which were associated with outcome at a significance of <0.1 were then added to the model, and likelihood ratio tests performed to determine the best fit model.

Analysis of co-morbidities

Time to culture positivity and drug sensitivity of M. tuberculosis isolates

Chi2 test for trend was used to examine the association between time to positivity of sputum culture and clinical outcome. Univariate logistic regression models were used to derive unadjusted odds ratios, the 95% confidence intervals and associated Wald p-values for the presence of drug resistance and clinical outcome.

HIV infection

Univariate logistic regression models were used to derive unadjusted odds ratios, the 95% confidence intervals and associated Wald p-values for the associations between clinical outcome and ART, length of time on ART, CD4 count and viral load.

Lung pathology

Cohen's kappa statistics were calculated to assess inter-reader correlation of x-ray and CT scan reporting. Simple proportions describing the patterns of acute and chronic lung disease on x-ray and CT scan were calculated. Fishers exact test was used to explore associations between patterns of acute lung disease and sputum smear and culture status, HIV status, gender, age and smoking. Univariate logistic regression models were used to derive unadjusted odds ratios, the 95% confidence intervals and associated Wald p-values for the presence of bronchiectasis, and successful TB treatment outcome. Multivariate logistic regression models were used to explore independent clinical predictors of bronchiectasis, and the associations between chronic lung disease and TB treatment outcome. Variables included in both of these models of chronic lung disease were predefined as age, gender, HIV status, TB status (confirmed or unconfirmed microbiologically) and smoking history. The logistic regression models were used to determine odds ratios, the 95% confidence intervals and associated Wald p-values for treatment outcomes in patients with chronic lung disease and the presence of bronchiectasis on CT thorax. The same predefined variables were used in multivariate analysis of the

associations with restrictive lung disease as well as analysis of the associations between chronic lung disease on CT thorax and abnormal spirometry.

Analysis of drug toxicities

Univariate logistic regression was used to derive unadjusted odds ratios, 95% confidence intervals and associated Wald p-values for ototoxicity and nephrotoxicity according to age, gender, BMI, HIV status, baseline renal function and ART status. Predefined variables used in a multivariate analysis of factors associated with ototoxicity were BMI, age, gender, HIV status and baseline renal function. Predefined variables in a multivariate analysis of factors associated with nephrotoxicity were BMI, age, gender HIV, and ART. All predefined variables in the study were chosen on the basis that there was a biological basis on which to suspect that they would be associated with outcome.

3.4 Results

3.4.1 Study participants

Between June 2013 and September 2014, 230 patients starting retreatment regimen for tuberculosis were screened for eligibility. After excluding 72 patients, 158 were enrolled in the study. The prevalence of microbiologically confirmed tuberculosis in the study population was 58% (figure 16).

Table 16 shows the baseline characteristics of the study population. The median age was 37 years, and 64.6% of patients were male. The majority (83.5%), had pulmonary TB, but the prevalence of extra-pulmonary TB was high in the group without confirmed TB at 34.8%. The category of treatment most commonly registered was ‘other’ (53.2%), and 95.5% of patients without a microbiological diagnosis fell into this category. Most patients had had one previous episode, although 3 patients were on at least their fourth episode of TB treatment. The HIV prevalence was 82.9%. The median CD4 count in the whole HIV positive study

population was 171 cells/mm^3, but it was lower in the group without a confirmed TB diagnosis (151 v 177 cells/mm^3). The prevalence of alcohol excess was high at 17.1%, and 26.6% of patients had a history of smoking.

Figure 16. Study enrolment

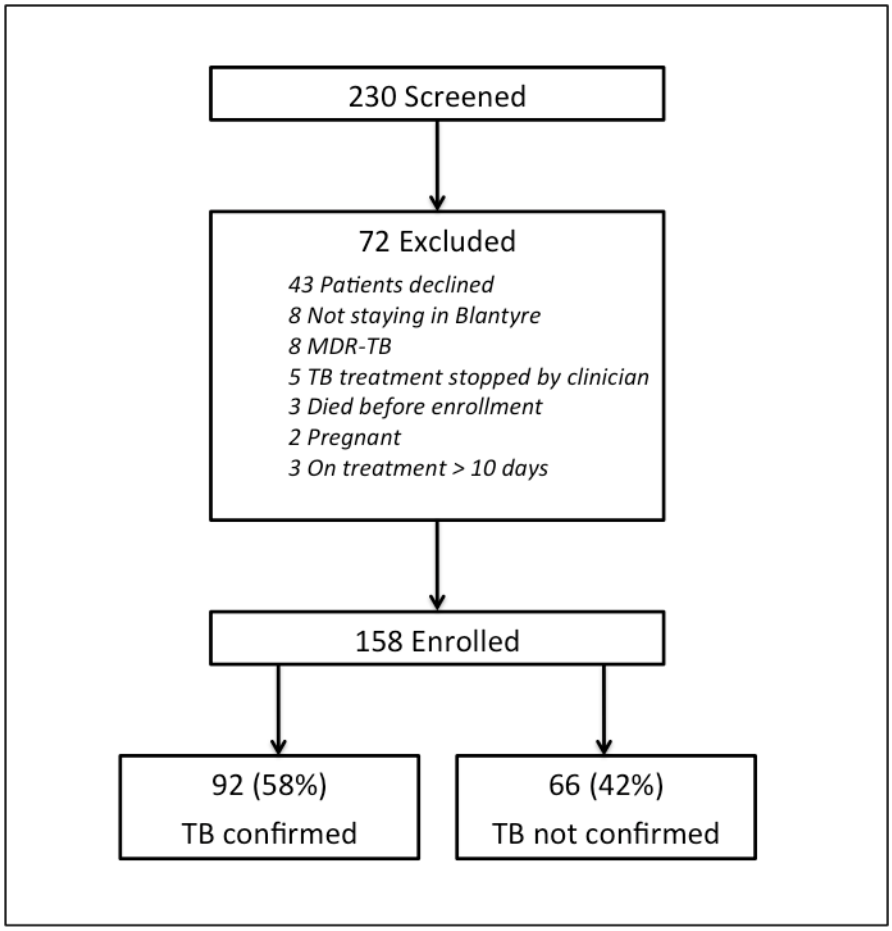


Table 16. Study population baseline characteristics

	Total study population n = 158 (%)	TB confirmed n = 92 (%)	TB not confirmed n = 66 (%)
Patient age (median, IQR)	37 (31-43)	38 (31-43)	35.5 (31-41)
Patient sex (% male)	102 (64.6)	64 (69.6)	38 (57.6)
TB Class			
Pulmonary	132 (83.5)	89 (96.7)	43 (65.2)
Extra-pulmonary	26 (16.5)	3 (3.3)	23 (34.8)
TB Category			
Relapse	62 (39.2)	62 (67.4)	0 (0.0)
Treatment after default	7 (4.4)	4 (4.6)	3 (4.5)
Fail	5 (3.2)	5 (5.4)	0 (0.0)
Other	84 (53.2)	21 (22.8)	63 (95.5)
Smear negative	57 (36.0)	17 (18.5)	40 (60.6)
Extra-pulmonary	27 (17.1)	4 (4.3)	23 (34.8)
No. of previous TB episodes			
1	138 (87.3)	78 (84.8)	60 (90.9)
2	17 (10.8)	11 (12.0)	6 (9.1)
>2	3 (1.9)	3 (3.2)	0 (0.0)
HIV status			
Negative	27 (17.1)	17 (18.5)	10 (15.2)
Positive	131 (82.9)	75 (81.5)	56 (84.5)
CD4 count (median, IQR)	171 (61-324)	177 (45-309)	151 (75-327)
ART failure (n=64)	24 (37.5)	11 (32.4)	13 (43.3)
Karnofsky score at baseline (median, IQR)	90 (80-100)	90 (80-90)	90 (90-100)
HR >100bpm	95 (60.1)	58 (63.0)	37 (56.1)
RR >20bpm	37 (23.4)	17 (18.5)	20 (30.3)
SBP <100mmHg	50 (31.7)	35 (38.0)	15 (22.7)
BMI			
≥18.5	36 (23.7)	14 (15.9)	22 (34.4)
16-18.4	75 (49.3)	49 (55.7)	26 (40.6)
<16	41 (27.0)	25 (28.4)	16 (25.0)
Anaemia	34 (22.2)	16 (17.8)	18 (28.6)
Diabetes	5 (3.3)	5 (5.6)	0 (0.0)
Renal impairment	52 (33.8)	33 (36.7)	19 (29.7)
Chronic Lung disease on CT Thorax (n=102)	90 (88.2)	57 (93.4)	33 (80.5)
Pulmonary function testing (n=103)			
Normal	34 (33.0)	19 (32.2)	15 (35.7)
Obstructive	6 (5.8)	1 (1.6)	5 (11.9)
Restrictive	62 (61.2)	41 (67.2)	22 (52.4)
Smoker			
Never	116 (73.4)	65 (70.7)	51 (77.3)
Former	41 (26.0)	26 (28.3)	15 (22.7)
Current	1 (0.6)	1 (1.1)	0 (0.0)
History of alcohol excess	27 (17.1)	15 (16.3)	12 (18.2)

ART failure = Antiretroviral failure, defined as HIV viral load >5000 copies/ml
HR = Heart rate; RR = Respiratory rate; SBP = Systolic blood pressure; BMI = Body mass index

3.4.2 Factors associated with clinical outcomes on TB retreatment

Patients with a microbiologically confirmed diagnosis of TB were not more likely to successfully complete TB retreatment (66.3% v 71.2%; OR 0.80, 95% CI 0.40-1.58). In the study cohort as a whole, 24.1% of patients died before completing treatment, but only 1.3% failed treatment and only 6.4% were lost to follow up or not evaluated (table 17).

Table 17. 8-month treatment outcomes in patients with confirmed and unconfirmed TB

	Total study population n = 158 (%)	TB confirmed n = 92 (%)	TB not confirmed n = 66 (%)
Treatment success	108 (68.4)	61 (66.3)	47 (71.2)
Cured	40 (25.3)	40 (43.5)	NA
Treatment completed	68 (43.0)	21 (22.8)	47 (71.2)
Treatment failed	2 (1.3)	1 (1.1)	1 (1.5)
Died	38 (24.1)	22 (23.9)	16 (24.2)
Lost to follow-up	8 (5.1)	6 (6.5)	2 (3.0)
Not evaluated	2 (1.3)	2 (2.2)	0 (0.0)

In univariate analysis, baseline anaemia and systolic hypotension were both significantly associated with poor end-of-treatment outcome (table 18). A likelihood ratio test suggested that a multivariate model which included hypotension and anaemia fit the data better than one which included only the predefined variables of age, gender and HIV (LRT p-value 0.01). After adjusting for age, gender, HIV status hypotension, and anaemia, hypotension but not anaemia remained significantly associated with outcome. Outcomes were worse in the categories 'Fail' and 'Other', but this difference was not statistically significant.

Table 18. Features associated with clinical outcome on TB retreatment

	Successful outcome n (%)	p-value	OR (95% CI)	p-value	aOR (95% CI)
Confirmed TB					
No	47/66 (71.2)				
Yes	61/92 (66.3)	0.51	0.80 (0.40-1.58)	0.55	0.80 (0.37-1.70)
TB site					
Pulmonary	93/132 (70.5)				
Extra-pulmonary	15/26 (57.7)	0.20	0.57 (0.23-1.36)	-	-
TB Category					
Relapse	47/63 (74.6)				
TAD	5/7 (71.4)	0.86	0.85 (0.15-4.83)		
Fail	3/5 (60.0)	0.48	0.51 (0.08-3.34)	-	-
Other	53/83 (63.9)	0.17	0.60 (0.29-1.24)	-	-
Age					
<30	22/32 (68.8)				
30-35	28/43 (65.1)	0.74	0.85 (0.32-2.25)	0.92	1.06 (0.36-3.11)
36-45	39/56 (69.6)	0.93	1.04 (0.41-2.67)	0.74	1.20 (0.40-3.57)
>45	19/27 (70.4)	0.89	1.08 (0.35-3.29)	0.85	1.12 (0.34-3.66)
Gender					
Female	34/56 (60.7)				
Male	74/102 (72.6)	0.13	1.71 (0.86-3.41)	0.32	1.48 (0.69-3.20)
HIV status					
Negative	21/27 (77.8)				
Positive	87/131 (66.4)	0.25	0.56 (0.21-1.50)	0.60	0.74 (0.24-2.30)
HR >100bpm					
No	47/63 (74.6)		-		
Yes	61/95 (64.2)	0.17	0.61 (0.30-1.24)	-	-
RR>20bpm					
No	64/95 (67.4)		-		
Yes	44/63 (69.8)	0.74	1.12 (0.56-2.23)	-	-
SBP<100mmHg					
No	82/108 (95.9)				
Yes	26/50 (52.0)	0.003	0.34 (0.17-0.70)	0.02	0.41 (0.19-0.87)
BMI					
≥18.5	23/36 (63.9)				
16-18.4	58/75 (77.3)	0.14	1.93 (0.81-4.60)	-	-
<16	24/41 (58.5)	0.63	0.80 (0.32-2.00)	-	-
Anaemia					
No	88/119 (74.0)		-		
Yes	18/34 (52.9)	0.02	0.40 (0.18-0.87)	0.11	0.50 (0.22-1.17)
Chronic Lung Disease on CT	11/12 (91.7)				
No	71/90 (78.9)	0.32	0.34 (0.04-2.80)	-	-
Yes					
Abnormal Spirometry					
No	32/34 (94.1)				
Yes	56/69 (81.2)	0.10	0.30 (0.06-1.27)	-	-
Diabetes					
No	101/146 (69.2)				
Yes	4/5 (80.0)	0.61	1.78 (0.19-16.4)	-	-
Renal impairment					
No	74/102 (72.5)				
Yes	31/52 (59.6)	0.11	0.56 (0.28-1.13)		-

** adjusted for age, gender, HIV, confirmed TB, hypotension, anaemia*

ART failure = Antiretroviral failure, defined as HIV viral load >5000 copies/ml

HR = Heart rate; RR = Respiratory rate; SBP = Systolic blood pressure; BMI = Body mass index

3.4.3 *M. tuberculosis* burden and drug sensitivity patterns

The median time to sputum culture positivity was 7.8 days (IQR 4.9-9.9 days). There was no significant association between time to culture positivity and clinical outcome (table 19).

Table 19. Time to sputum culture positivity

	Successful outcome n (%)	p-value	OR (95% CI)
TTP (days)			
≤ 3	5/8 (62.5)		
3-7	19/29 (65.5)	0.87	1.14 (0.22-5.78)
>7	26/36 (72.2)*	0.59	1.56 (0.31-7.78)

** Chi2 test for trend p-value 0.499*

Of the patients who were sputum culture positive, 52 isolates were successfully recovered for phenotypic drug sensitivity testing (table 20). Only five patients (9.6%) had M. tuberculosis isolates cultured from sputum which showed any drug resistance on testing. The commonest drug resistance was to ethambutol (5.8%) and isoniazid (3.9%). After screening for rifampicin resistance with GXP, there was no undiagnosed rifampicin resistance. No streptomycin resistance was detected, and no isolates had resistance to more than a single drug.

Table 20. Drug sensitivity patterns and TB treatment outcomes

Resistance	Total n = 52	Successful outcome with sensitive isolate n (%)	Successful outcome with resistant isolate n (%)	p-value	OR (95% CI)
Rifampicin	0 (0.0)	36 (69.2)	-	-	-
Isoniazid	2 (3.9)	35 (70.0)	1 (50.0)	0.56	0.43 (0.25-7.31)
Ethambutol	3 (5.8)	34 (69.4)	2 (66.7)	0.92	0.88 (0.07-10.50)
Streptomycin	0 (0.0)	36 (69.2)	-	-	-
Any resistance	5 (9.6)	33 (70.2)	3 (60.0)	0.64	0.64 (0.10-4.23)

3.4.4 Co-morbidity in patients on TB retreatment

The prevalence of baseline co-morbidity in patients on TB retreatment according to TB diagnosis is summarised briefly in table 16. Baseline anaemia was common (22.2%), and associated in univariate but not multivariate analysis with poor treatment outcome (table 18). The prevalence of baseline renal impairment was 33.8%, but this was not associated with poor treatment outcome (OR 0.56, 95% CI 0.28-1.13). Diabetes was only present in 3.3% of patients, and was not associated with unsuccessful treatment outcome either (OR 1.78, 95% CI 0.19-16.4).

3.4.4.1 HIV infection

HIV prevalence in this cohort of patients on TB retreatment was high at 82.9%. Although not significant on statistical testing, it is of note that only 66.4% of HIV positive patients successfully completed treatment compared to 77.8% of HIV negative patients. Factors associated with treatment outcome amongst HIV positive patients are shown in table 21. Only 55.4% of patients with CD4 count <100 cells/mm^3 successfully completed treatment, compared to 72.6% of those with CD4 count ≥100 cells/mm3. Patients with ART failure had only a 50.0% chance of successful treatment outcome, in comparison to 70.1% for patients who were not diagnosed with ART failure (OR 0.43 (95% CI 0.17-1.05; p-value 0.09).

Although there was no difference in treatment outcome between patients who were and who were not on ART, there is a suggestion that length of time on ART may be associated with risk of unsuccessful TB treatment. Both patients who had been on ART for less than 6 months and those on ART longer than 12 months had lower (but not significant on statistical testing) probability of treatment success than those who had been on ART for between 6 and 12 months (65.4%, 63.5% and 76.9% respectively).

Table 21. Factors associated with clinical outcome amongst HIV positive patients

	Successful outcome n (%)	OR (95% CI)	p-value
ART			
No	20/29 (68.9)		
Yes	67/102 (66.7)	0.86 (0.35-2.09)	0.74
Length of time on ART			
<6 months	17/26 (65.4)		
6 – 12 months	10/13 (76.9)	1.76 (0.39-8.09	0.47
>12 months	40/63 (63.5)	0.88 (0.34-2.29)	0.80
CD4 count			
<100	26/47 (55.4)		
≥100	61/84 (72.6)	2.14 (1.01-4.53)	0.06
Viral load			
Not detectable	75/107 (70.1)		
Detectable	12/24 (50.0)	0.43 (0.17-1.05)	0.09

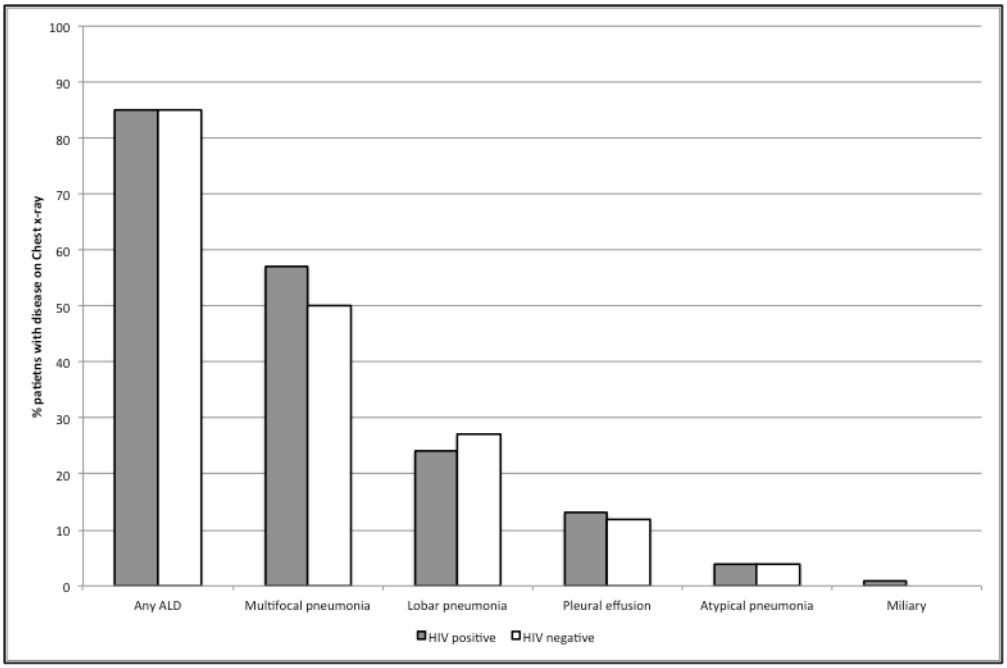
3.4.4.2 Lung Disease

A total of 102 CT thorax scans and 146 chest x-rays were performed. Reasons why imaging was not performed included primarily that the patient was not well enough or died prior to an x-ray or CT being performed; and that there were long periods when the CT scanner was not working. All CT and plain x-ray images were reviewed by two radiologists. The kappa statistics for agreement between the two reporters were 0.60 for acute lung disease on CXR; 0.66 for the presence of changes consistent with active TB on CXR; and 0.45 for chronic lung disease on CT. Results presented are based on consensus reports compiled by discussion between the two radiologists.

Acute Lung Disease

Acute changes on plain chest x-ray were seen in 124/146 (84.9%) of patients. The commonest finding was multifocal pneumonia (55.9%), followed by lobar pneumonia (24.1%); pleural effusion (12.4%); atypical pneumonia (4.4%); miliary pattern (0.7%) and other forms of acute lung injury (6.2%). All 4 cases of miliary TB which were seen on CT thorax were not visible on plain chest x-ray. Figure 17 demonstrates the frequency of acute lung disease seen on chest x-ray according to HIV status. The patterns of acute lung disease did not vary significantly according to HIV status, age or gender. Multifocal pneumonia was more common in people with a history of smoking (73.7% v 49.5%; RR 1.48 95%, CI 1.13-1.95; p-value 0.01), but smoking was not associated with any other acute chest x-ray changes.

Figure 17. Acute lung disease on chest x-ray according to HIV status



Chronic Lung Disease

Of 102 patients who had CT thorax performed, 88 (86%) were shown to have some form of chronic lung disease. Bronchiectasis was present in 62 patients; features of emphysema in 22; scarring in 20; destroyed lung in 19; and features consistent with pulmonary artery hypertension in 2. Of the 62 patients with bronchiectasis on CT scan, 55% had peripheral disease, 7% had central disease and 38% had both peripheral and central disease. In 47% of cases, bronchiectasis was associated with traction, and in 45% it was associated with volume loss (figure 18). The majority (71%) of bronchiectasis was classified as cystic type bronchiectasis (figure 19). CT thorax was able to help distinguish changes consistent with active cavity formation from patterns of chronic cystic bronchiectasis (figure 20). Patients with bronchiectasis were more likely to have changes consistent with acute pulmonary disease on chest x-ray than those without bronchiectasis (95.2% v 71.1%, p-value 0.002). In 8/19 (42%) of patients with destroyed lung, more than 25% of the lung parenchyma was affected (figure 21). Of those with lung scarring on CT, the changes were consistent with post-TB scarring in 82% (figure 22).

There were 36 (35%) patients who had evidence of pleural thickening on CT thorax, of whom 8 had bilateral disease. Apical disease was present in 18 patients, basal disease in 16, and 2 patients had both basal and apical pleural thickening. Only 1 patient, a 44 year old HIV-positive man with culture-negative TB, had pleural plaques.

32/62 (52%) of patients with bronchiectasis on CT thorax had no evidence of bronchiectasis on plain chest x-ray (figures 23 & 24). Similarly, 9/22 (41%) of emphysema (figure 22); 29/79 (37%) of scarring; and 5/19 (26%) of destroyed lung seen on CT was not visible on plain x-ray.

Figure 18. Coronal CT images demonstrating cystic bronchiectasis in the left upper lobe with volume loss.

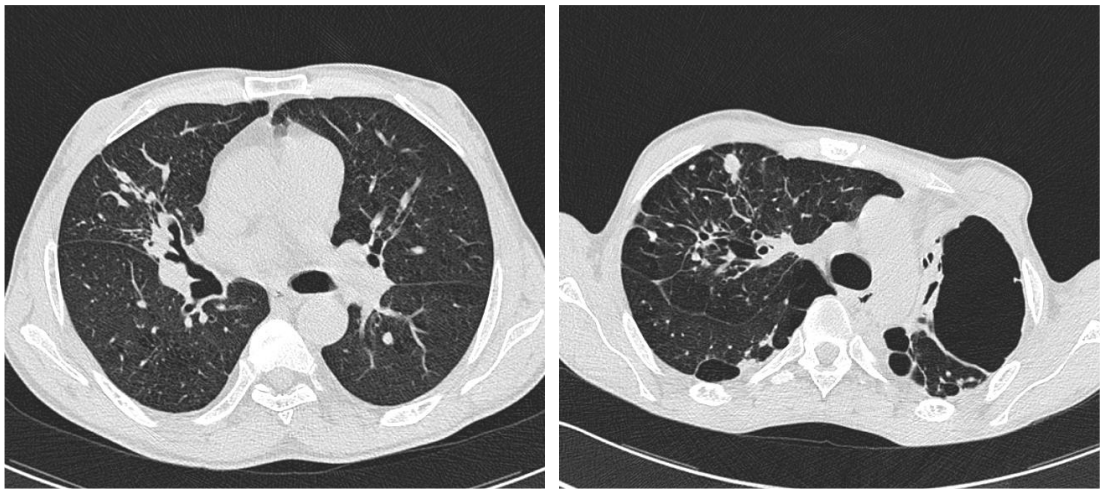


Figure 19. Axial image showing bilateral cystic bronchiectasis, demonstrating connection between large cysts and dilated airway (white arrows) as well as smaller cysts (black arrows). In addition, active nodular disease is seen in the apex of the left lower lobe (striped arrow).

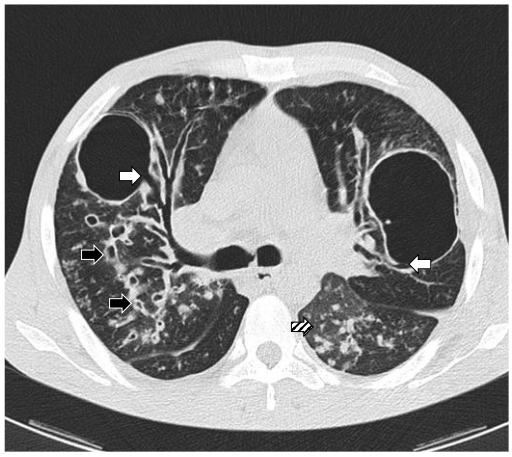


Figure 20. Axial and coronal CT images showing bilateral upper lobe cavitation, with surrounding nodular consolidation, consistent with active disease.

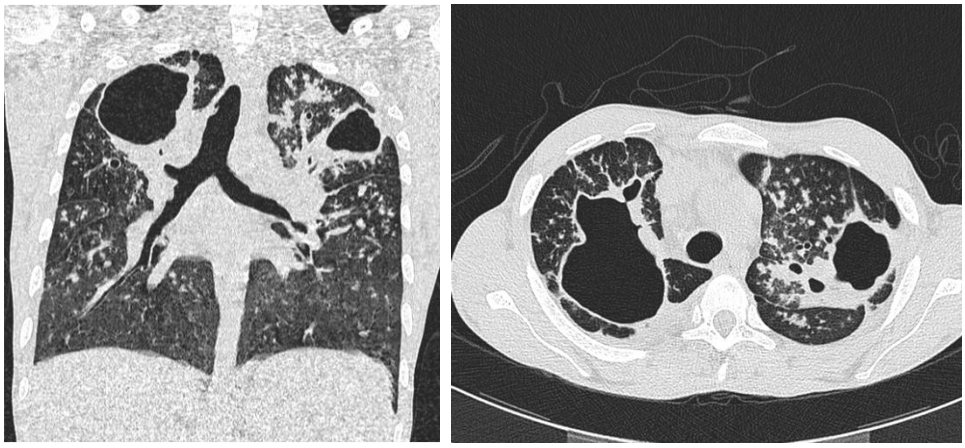


Figure 21. Axial and coronal images of a destroyed left upper lobe, involving approximately 25 – 50% of the lungs. Nodular and consolidative active disease is present in the right lung and left lower lobe.

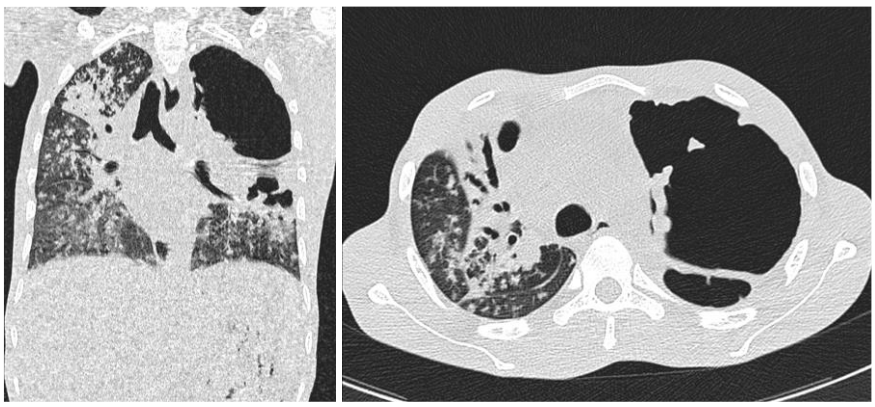


Figure 22. Chest X-ray showing hyperinflation and corresponding CT images of panlobular emphysematous change (white arrows), as well as chronic nodular and linear scarring in the right upper lobe (black arrows).

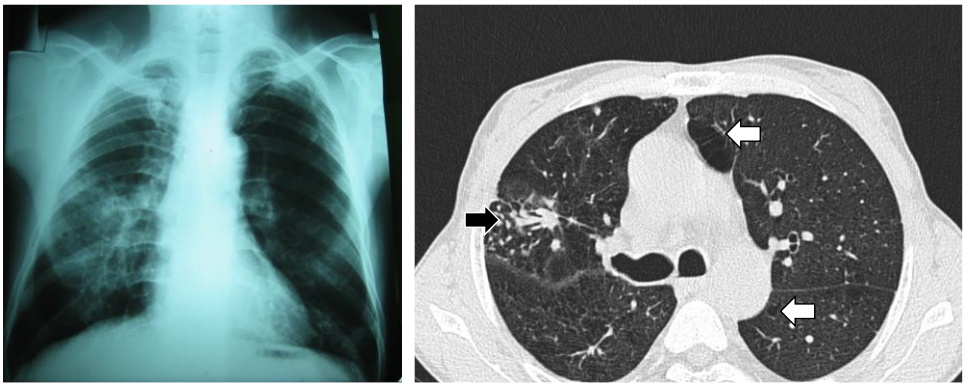


Figure 23. Chest X-ray and coronal reformat of CT. There is bilateral upper lobe central cylindrical bronchiectasis (white arrows), which are not visible on the Chest X-ray. There is also dense nodular and linear scarring on CT images which are not seen on Chest X-ray (black arrows).

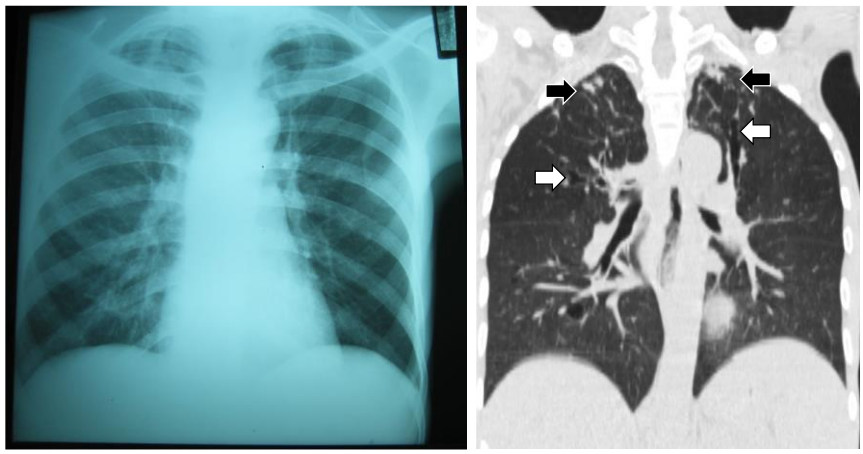


Figure 24. Chest X-ray and coronal CT image of extensive, longstanding cystic bronchiectasis in the left upper lobe, which is not visible on Chest X-ray.

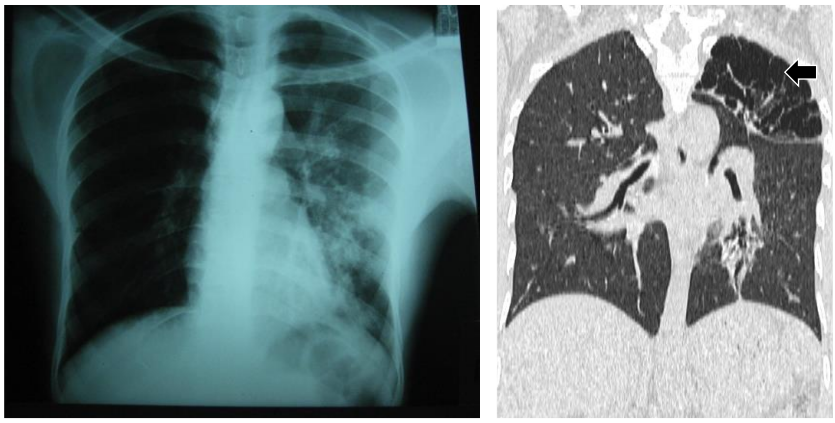


Figure 25 shows the proportions of patients with different types of chronic lung disease on CT thorax according to their baseline sputum culture result. There were no significant differences in the rates of chronic lung disease between those patients who were sputum culture positive and those who were sputum culture negative. Overall 92 % of patients with culture positive TB and 97% of patients with culture negative TB had some form of chronic lung disease. Of note, the proportion of patients with bronchiectasis was higher amongst patients with culture positive TB (78%) than culture negative TB (59%) (RR 1.90, 95% CI 0.99-3.69; p-value 0.08) The patterns of chronic lung pathology were similar when analysed by sputum smear status.

Bronchiectasis was associated with being HIV negative, having confirmed TB and with a history of smoking (table 22). The associations remained significant after additionally adjusting for age and gender. No other pattern of chronic lung disease was associated in multivariate analysis with HIV status, TB status, smoking, age or gender.

Figure 25. Proportion of patients with chronic lung disease according to baseline TB culture

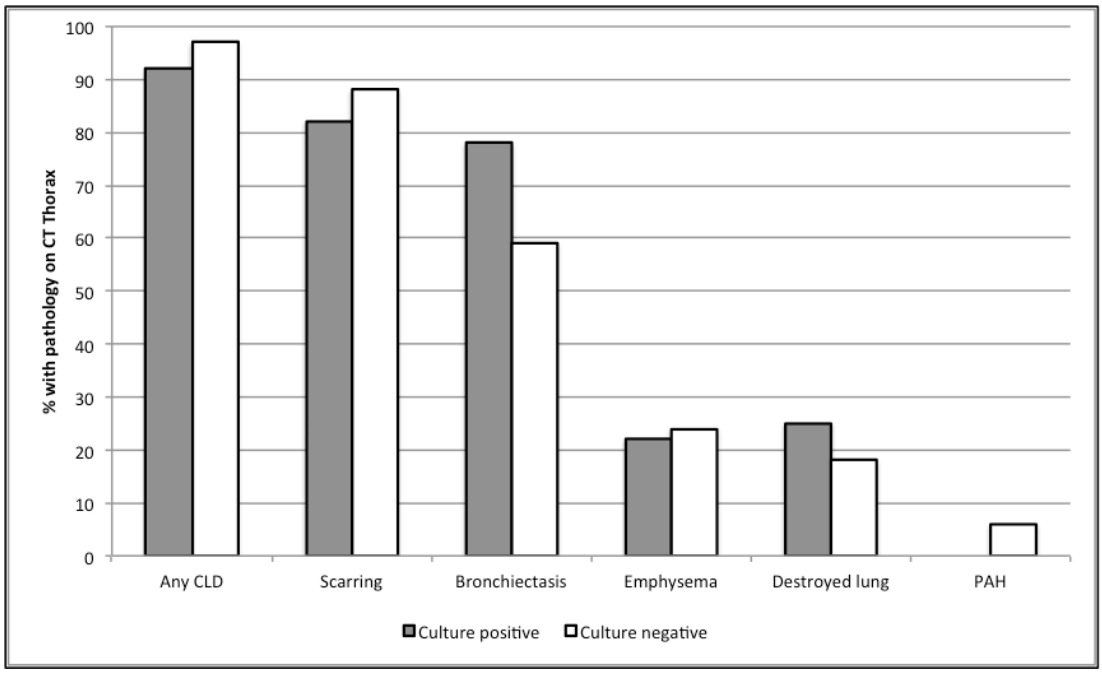


Table 22. Factors associated with bronchiectasis

	Bronchiectasis n (%)	p-value	OR (95% CI)	p-value	aOR* (95%CI)
Age					
<30	13/18 (72.2)				
30-35	14/31 (45.2)	0.07	0.32 (0.09-1.11)	0.36	0.46 (0.09-2.36)
36-45	23/37 (62.2)	0.46	0.63 (0.19-2.16)	0.79	1.25 (0.24-6.40)
>45	12/16 (75.0)	0.85	1.15 (0.25-5.33)	0.63	1.56 (0.25-9.58)
Gender					
Male	48/74 (64.9)				
Female	14/28 (50.0)	0.17	1.85 (0.76-4.46)	0.44	1.55 (0.50-4.60)
Smoking					
Never	37/71 (52.1)				
Former/current	25/31 (80.6)	0.01	3.83 (1.40-10.46)	0.02	4.60 (1.35-15.67)
Confirmed TB					
No	17/41 (41.5)				
Yes	45/61 (73.8)	0.001	4.00 (1.71-9.23)	0.01	3.60 (1.38-9.36)
HIV					
Negative	18/21 (85.7)				
Positive	44/81 (54.3)	0.01	0.20 (0.05-0.73)	0.04	0.19 (0.04-0.95)

** Adjusted for age, gender, smoking, HIV, confirmed TB*

Table 23. Associations between chronic lung disease patterns and clinical outcome

	Successful outcome n (%)	p-value	OR (95% CI)	p-value	aOR* (95% CI)
Any CLD					
No	11/12 (91.7)				
Yes	71/90 (78.9)	0.32	0.34 (0.04-2.80)	0.24	0.26 (0.03-2.45)
Bronchiectasis					
No	35/40 (0.88)				
Yes	47/62 (0.76)	0.15	0.45 (0.15-1.35)	0.17	0.41 (0.19-1.47)
Emphysema					
No	64/80 (0.80)				
Yes	18/22 (0.82)	0.85	1.13 (0.33-3.79)	0.91	0.93 (0.25-3.42)
Destroyed lung					
No	70/83 (0.84)				
Yes	12/19 (0.63)	0.04	0.32 (0.11-0.96)	0.08	0.32 (0.09-1.13)
Scarring					
No	18/20 (0.90)				
Yes	64/82 (0.78)	0.24	0.40 (0.08-1.86)	0.09	0.23 (0.04-1.28)

** Adjusted for age, gender, smoking, HIV, confirmed TB*

The study was not powered to detect significant associations between lung disease and clinical outcome. However, table 23 demonstrates that although not statistically significant, the probabilities of successful treatment outcome were lower for patients with any chronic lung disease, bronchiectasis, scarring. Destroyed lung was associated with unsuccessful clinical outcome on univariate analysis but after controlling for age, gender, smoking, HIV and confirmed TB the adjusted OR was 0.32 with 95% CI 0.09-1.13.

Chronic Lung Disease in relation to Pulmonary Function

103 patients had spirometry performed after 2 months of TB treatment. Only 34 (33%) had normal pulmonary function: 63 (61.2%) had restrictive pulmonary deficit and 6 (5.8%) had obstructive deficit. Restrictive pulmonary function was not significantly associated with age, sex, BMI, smoking, HIV or number of previous TB episodes (table 24). The prevalence of restrictive pulmonary function in patients with BMI less than 16 was 77%, which was higher than in those with BMI between 16 and 18.5 or in those with BMI greater than 18.5 (57.1% and 56.0% respectively), however this difference was not statistically significant (chi^2 test for trend p-value 0.15). Similarly, the prevalence of restrictive pulmonary deficit was higher in smokers (72.4% v 56.8%), but the difference was not statistically significant.

Of the 6 patients with obstructive pulmonary deficit, only one had a history of smoking. Half of the patients were male; 4/6 were HIV positive; 4/6 had BMI greater than 16; and 3/6 were older than 45 years.

Successful treatment outcome was seen in 52/63 (82.5%) of patients with restrictive pulmonary deficit, in comparison 36/40 (90.0%) without restrictive deficit (OR 0.52, 95% CI 0.15-1.78; p-value 0.39). There were few patients with obstructive deficit, however the treatment success rate in this group was 4/6 (66.7%) compared to those without obstruction in whom 84/97 (86.6%) successfully completed treatment (OR 0.31, 95% CI 0.05-1.86; p-value 0.21).

Table 24.Factors associated with restrictive pulmonary deficit

	Restrictive pulmonary deficit n (%)	p-value	OR (95% CI)	p-value	aOR* (95% CI)
Age					
<30	14/21 (66.7)				
30-35	20/27 (74.1)	0.58	1.43 (0.41-4.99)	0.81	1.19 (0.28-4.99)
36-45	19/35 (54.3)	0.36	0.59 (0.19-1.82)	0.32	0.49 (0.12-2.00)
>45	10/20 (50.0)	0.28	0.50 (0.14-1.77)	0.29	0.47 (0.12-1.92)
Gender					
Female	21/36 (58.3)				
Male	42/67 (62.7)	0.67	1.20 (0.52-2.74)	0.78	1.16 (0.42-3.21)
Smoking					
Never	42/74 (56.8)				
Former/current	21/29 (72.4)	0.15	2.00 (0.79-5.10)	0.12	2.39 (0.79 – 7.16)
BMI					
≥ 18.5	14.25 (56.0)				
16.18.4	32/56 (57.1)	0.92	1.05 (0.40-2.71)	0.92	1.06 (0.37-3.02)
<16	17/22 (77.3)	0.13	2.67 (0.75-9.53)	0.22	2.34 (0.60-9.11)
Confirmed TB					
No	22/42 (52.4)				
Yes	41/62 (67.2)	0.13	1.86 (0.83-4.18)	0.11	2.11 (0.85-5.20)
HIV					
Negative	11/19 (57.9)				
Positive	52/84 (61.9)	0.75	1.18 (0.43-3.25)	0,46	1.64 (0.07-4.06)

** Adjusted for age, gender, smoking, HIV, confirmed TB*

Of patients who had spirometry performed at 2 months, repeat testing was done after 8 months of TB treatment in 58. Out of the 33 patients in this group who had restrictive pulmonary function at 2 months, 19 (57.6%) still had restrictive deficit at 8 months; 4 had developed evidence of obstructive disease; and 10 had normal spirometry. Obstructive pulmonary function remained in 3 out of the 4 who had had obstruction at 2 months. There were 21 patients who had normal spirometry on initial testing, of whom 2 developed obstruction and 1 developed restriction.

There were only 77 patients who had both CT thorax and spirometry at 2 months, therefore the study lacked power to determine whether spirometry was a useful predictor of radiologically confirmed chronic lung disease. Nonetheless, the data examining these associations are presented in table 25, and they suggest that patients with either bronchiectasis or destroyed lung were more likely to have abnormal pulmonary function. Of patients with bronchiectasis, 75.0% had abnormal

spirometry, compared to 55.2% without; and of patients with destroyed lung, 92.3% had abnormal spirometry, compared to 62.5% without.

Table 25. Associations between chronic lung disease patterns on CT thorax and abnormal respiratory function

	Abnormal spirometry	p-value	OR (95% CI)	p-value	aOR* (95% CI)
Bronchiectasis					
No	16/29 (55.2)				
Yes	36/48 (75.0)	0.08	2.43 (0.91-6.50)	0.07	3.06 (0.91-10.36)
Emphysema					
No	40/60 (66.7)				
Yes	12/17 (70.6)	0.76	1.20 (0.37-3.88)	0.64	1.35 (0.38-4.76)
Destroyed lung					
No	40/64 (62.5)				
Yes	12/13 (92.3)	0.07	7.2 (0.88-58.90)	0.13	5.53 (0.62-49.51)
Scarring					
No	9/12 (75.0)				
Yes	43/65 (66.2)	0.55	0.65 (0.16-2.65)	0.59	0.64 (0.13-3.26)

** Adjusted for age, gender, smoking, HIV, confirmed TB*

3.4.5 Drug toxicities associated with TB retreatment

Overall 80/158 (50.6%) patients experienced at least one drug side effect during the first 2 months of TB retreatment, with streptomycin toxicity being common (table 26). Six patients (4.4%) experienced drug induced liver injury, and 1 had Stevens Johnsons Syndrome requiring interruption of treatment. There were no significant associations between treatment outcome and nephrotoxicity or ototoxicity. Four out of the six patients with drug induced liver injury died (RR for death 5.78, 95% CI 2.75-12.10; p-value 0.004).

Table 26. Drug toxicity during the first 2 months of TB retreatment

	Total n (%)	Successful outcome with no toxicity n (%)	Successful outcome with toxicity n (%)	p-value	OR (95% CI)
Ototoxicity	28/78 (35.9)	43/50 (86.0)	23/28 (82.1)	0.65	0.75 (0.21-2.63)
Nephrotoxicity	19/130 (14.6)	88/111 (79.3)	15/19 (79.0)	0.97	0.98 (0.30-3.24)
Neuropathy	51/127 (40.2)	62/76 (81.6)	40/51 (78.4)	0.66	0.82 (0.34-1.99)
DILI	6/136 (4.4)	104/130 (80.0)	2/6 (33.3)	0.02	0.13 (0.02-0.72)
SJS	1/158 (0.6)	107/157 (68.2)	1/1 (100.0)	1.0	-

DILI = Drug Induced Liver Injury
SJS = Stevens Johnsons Syndrome

3.4.5.1 Ototoxicity

Results of audiological evaluation on 78 patients who were assessed at baseline and 2 months demonstrated that 28 (35.9%) developed high frequency hearing loss during the period in which they received streptomycin. Vestibular function was assessed in 27 patients, of whom 3 (11.1%) developed features suggestive of vestibulotoxicity in addition to high frequency hearing loss. The development of ototoxicity was not associated with BMI, age, gender, HIV status or baseline renal impairment (table 27). Hearing loss was measured again at 8 months in 46 patients. Of the 14 patients in this group who had developed ototoxicity whilst on streptomycin, 6 (42.9%) still had high frequency hearing loss at the end of treatment, 6 months after completing streptomycin.

Table 27. Risk factors associated with ototoxicity

	Ototoxicity n (%)	p-value	OR (95% CI)	p-value	aOR* (95% CI)
BMI					
>=18.5	8/21 (38.1)				
16.18.4	13/41 (31.7)	0.62	0.75 (0.25-2.26)	0.57	0.70 (0.21-2.39)
<16	7/16 (43.8)	0.73	1.26 (0.34-1.75)	0.48	1.70 (0.39-7.46)
Age					
<30	8/15 (53.3)				
30-35	7/25 (28.0)	0.11	0.34 (0.09 -1.30)	0.41	
36-45	8/25 (32.0)	0.19	0.42 (0.11-1.54)	0.59	0.52 (0.11-2.45)
>45	5/13 (38.5)	0.43	0.55 (0.12-2.47)	0.57	0.65 (0.12-3.16)
Gender					
Female	12/28 (42.9)				
Male	16/50 (32.0)	0.34	0.63 (0.24-1.63)	0.11	0.37 (0.11-1.26)
HIV					
Negative	7/12 (58.3)				
Positive	21/66 (31.8)	0.09	0.33 (0.09-1.17)	0.10	0.26(0.05-1.29
Baseline renal function					
Normal	20/60 (33.3)				
Abnormal	8/18 (44.4)	0.39	1.6 (0.55-4.68)	0.96	0.97 (0.11-1.26)

** adjusted for BMI, age, gender, HIV status, and baseline renal function*

3.4.5.2 Nephrotoxicity

Renal function was assessed at the start of treatment and after 2 months in 130 patients, of whom 19 (14.6%) developed renal impairment. Nephrotoxicity was not associated with BMI, age, gender, HIV status or ART (most patients were on tenofovir containing regimens which are known to be associated with kidney disease) (table 28).

Table 28. Risk factors associated with nephrotoxicity

	Nephrotoxicity n (%)	p-value	OR (95% CI)	p-value	* aOR (95% CI)
BMI					
>=18.5	3/31 (9.7)				
16.18.4	10/67 (14.9)	0.48	1.64 (0.42-6.43)	0.36	2.13 (0.42-10.69)
<16	6/32 (18.8)	0.31	2.15 (0.49-9.51)	0.19	3.24 (0.56-10.80)
Age					
<30	5/26 (19.2)				
30-35	4/39 (10.3)	0.31	0.48 (0.12-1.99)	0.39	0.51 (0.11-2.42)
36-45	7/43 (16.3)	0.75	0.82 (0.23-1.90)	0.92	1.10 (0.22-5.25)
>45	3/22 (13.6)	0.61	0.66 (0.14-3.16)	0.83	0.83 (0.15-4.53)
Gender					
Female	9/44 (20.5)				
Male	10/86 (11.6)	0.18	0.51 (0.19-1.37)	0.08	0.36 (0.12-1.14)
HIV					
Negative	4/25 (16.0)				
Positive	15/105 (14.3)	0.83	0.88 (0.26-2.91)	0.89	0.88 (0.15-5.28)
On ART at start					
No	8/49 (16.3)				
Yes	11/81 (13.6)	0.67	0.81 (0.30-2.17)	0.44	0.59 (0.15-2.25)

** adjusted for BMI, age, gender, HIV status and ART*

3.5 Discussion

This study has demonstrated once again that outcomes on Category II retreatment regimen are poor with only 68.4% of patients successfully completing treatment, but, more importantly, it also provides new insights into some of the reasons which may explain these poor outcomes. In contrast to the assumption made during the design of the study, microbiological confirmation of TB was not associated with unsuccessful treatment outcome (66.3% successful treatment in patients with confirmed TB compared to 71.2% successful treatment in patients without confirmed TB). A key finding of the study is that the prevalence of drug resistance in this cohort of patients on TB retreatment was low, and not associated with poor outcome. After adjusting for age, gender and HIV status the only factor associated with unsuccessful treatment outcome was hypotension at presentation. However, the prevalence of medical co-morbidities which may contribute to poor treatment outcomes was high, with 82.9% of patients being HIV infected, 88.2% having chronic lung disease on CT thorax, 33.8% having baseline renal impairment, and 22.2% having anaemia. The incidence of drug toxicity during the first two months of treatment was also high, with 50.6% of all patients experiencing at least one drug side effect. The incidence of streptomycin induced toxicity is of particular concern as 35.9% of patients developed ototoxicity and 14.6% developed nephrotoxicity.

The high mortality (24.1%) seen in this cohort is alarming, and higher than many previous studies. Of the studies included in the systematic review of outcomes on TB retreatment in chapter 1, mortality rates varied between 6%- 25%. Only one study reported a mortality rate of higher than 20% [112], and interestingly this study was also conducted in Malawi. The high death rate can perhaps be viewed in conjunction with the very low rates of default and undocumented treatment outcomes. In studies which have followed up patients recorded as having defaulted from TB and/or HIV treatment in Africa, the true outcome is frequently death [353, 354]. It is possible that because this was a prospective study, in which patients and guardians built good relationships with the study team, the documentation of

treatment outcome was more accurate and death as a true outcome was more reliably determined.

3.5.1 Microbiological factors

Unlike many other countries with a high TB incidence, Malawi has a **low prevalence of drug resistant tuberculosis**. This was demonstrated in a national survey of drug resistance conducted in 2010 [58], and has been shown again 4 years later in this study. Of the 52 samples which were tested for drug resistance, only 3 (5.8%) had ethambutol resistance and 2 (3.9%) had isoniazid resistance. In the debate surrounding the management of patients with recurrent TB, the level of drug resistance in a particular setting is a crucial factor - it determines not only how to manage the risk of MDR-TB and which empirical drug regimen should be used for patients with recurrent TB who do not have MDR-TB, but also how likely it is that drug resistance accounts for poor clinical outcomes. Here, it is seen that not only was the prevalence of any form of drug resistance only 9.6%, but also that drug resistance was not associated with poor outcome (although numbers may have been too small to demonstrate any association). After using GXP to detect rifampicin resistance in sputum samples collected at the start of treatment, no additional cases of rifampicin resistance were found using phenotypic drug sensitivity testing, which is reassuring. It is unexpected that no streptomycin resistance was found, as it was the second commonest drug resistance pattern after isoniazid in the recent survey of drug resistance in Malawi. It must be noted as a weakness of the study that after storage, transport and re-culture of samples, only 52 isolates were tested for resistance, and it is possible that patterns in those samples not re-cultured may have been different.

It is perhaps surprising that microbiologically **confirmed TB was not predictive of clinical outcome,** as a number of previous studies have found that patients with smear and/or culture negative TB did worse than those with laboratory confirmed TB [341, 342]. The difference in outcomes has always been ascribed primarily to the fact that patients treated empirically for tuberculosis may not have TB, but rather

have other conditions which remain undiagnosed and therefore untreated [114]. The possibility of 'false positive' TB diagnoses is of particular importance in the group of patients classified as 'other' in whom fewer than 5% had a confirmed TB diagnosis, and in whom treatment outcomes were particularly poor (63.9% success rate). Without microbiological evidence of tuberculosis, it is impossible to know how many people prescribed treatment empirically actually have tuberculosis, and it is important to recognise the potential for harm caused by both undertreating the true pathology and exposing patients to toxic anti-tuberculous drugs.

One possible explanation for the discrepant result in this study is that, compared to new patients, patients on retreatment regimen have a high prevalence of multiple concurrent diagnoses, regardless of whether or not they have confirmed tuberculosis, and that co-morbid disease is common even in those who do have definite TB. In settings with high HIV prevalence, another reason for poorer outcomes in patients without microbiologically confirmed TB is the fact that HIV is associated with being sputum smear/culture negative and also with poorer clinical outcome due to other HIV related pathology [355, 356]. As the HIV prevalence in this cohort was so high (82.9%), and similar in both groups, the potential for HIV to have a differential effect on outcomes in those with and without confirmed TB was probably less significant. Nevertheless, patients who are sputum smear/culture negative are more likely to have disseminated disease and therefore do worse. Indeed extra-pulmonary disease was more common in those without a microbiological diagnosis (43.8% v 3.3%), and although not significantly associated with outcome, 70.5% of patients with pulmonary TB completed treatment, compared to only 57.7% with extra-pulmonary disease. Patients in this study were defined as having EPTB according to their TB registration status, but were not further categorised into those who simply had TB affecting an extra-pulmonary site and those who had truly disseminated disease. Had mycobacterial blood cultures been routinely performed it might have been easier to make this distinction, and to explore the spectrum of 'extra-pulmonary' disease further.

Unlike previous studies [357, 358], an association between **time to positivity** of sputum cultures and clinical outcome was not demonstrated in this study. It would be predicted that the higher mycobacterial load which is represented by early TTP would cause a more aggressive clinical picture. In this study data on TTP was available for only 73 samples, which may explain why the statistical test for trend was not significant. A different explanation might be that HIV prevalence in this cohort was high. HIV may affect the TTP, as it has previously been associated with delayed increase in TTP over time [359].

3.5.2 Medical co-morbidity

The finding that **hypotension at presentation is predictive of poor clinical outcome** is in keeping with previous literature [360, 361]. In tuberculosis, there are several potential mechanisms underlying the development of hypotension. Low blood pressure is likely to be associated with disseminated disease, although in this cohort hypotension was prevalent both in patients with microbiologically confirmed TB and those treated empirically (prevalences of hypotension being 38.0% and 22.7% respectively). *Mycobacterium tuberculosis septic shock* has been defined as 'positive identification of mycobacteria by microscopy or culture from sputum, body fluids and tissues as well as the absence of another more plausible pathogen in combination with sepsis syndrome and appropriate clinical suspicion,' and has been associated with an in-hospital mortality of 79.2% in one study [362]. It is also well reported that co-infection with other bacteria is common in patients with tuberculosis, many of which may cause bacteraemia and septic shock, and contribute to poor clinical outcomes [363, 364]. Finally, direct infection of the adrenal glands by *M. tuberculosis* can result in Addison's syndrome, which presents with hypotension [365, 366]. A study previously performed in Blantyre did not demonstrate a high prevalence of adrenal insufficiency in new smear positive patients [367], but another from Tanzania reported 32% of patients with chronic tuberculosis had an impaired cortisol response and that this was associated with hypotension [368]. In general, it is to be expected that patients who present acutely unwell with TB will do worse than those who are ambulatory, and a study

conducted at QECH in 2011 found that low BMI and high respiratory rate at presentation were independently associated with poor outcome during the intensive phase of treatment [364]. A number of studies have demonstrated that poor functional status at presentation is a predictor of unsuccessful treatment outcome, with higher mortality rates in sicker patients [369, 370].

Severe anaemia, defined as Hb <8g/dL was common, affecting 22.2% of patients overall, and was more prevalent in patients with extra-pulmonary disease (28.6% v 17.8%). Had anaemia been defined in the study protocol as Hb <10g/dL as some previous studies have done [219, 223], the overall prevalence of anaemia would have been even higher at 44.4%. Severe anaemia was associated with poor outcome on univariate but not multivariate analysis at a significance level of 0.05. However, it is possible that the study was simply underpowered in this respect, as multiple other studies have shown anaemia to be independently associated with poor outcome on TB treatment in both HIV positive and HIV negative patients [218, 369, 371]. Baseline **renal impairment** was also prevalent (33.8%), but not associated with outcome. Once again, it is possible that the study was underpowered to detect an association, as the absolute treatment success rate was higher in those with renal impairment (72.5% compared to 59.6%).

Only five patients had **diabetes mellitus** (3.3%). All five had microbiologically confirmed tuberculosis, which is in keeping with previous literature suggesting that diabetes is associated with increased cavitation and smear positivity [203, 205]. Only three out of the five patients were HIV positive. However, the low prevalence of diabetes in this cohort conforms to the suggestion that the TB-DM association is not as much of a concern in Africa as it is in Asia, America, and Europe. Other research has reported that TB studies conducted in Africa tend to recruit younger patients in whom non-communicable diseases such as diabetes are less prevalent [372, 373]. Nevertheless, the implementation of a programmatic approach TB-DM which is currently being advocated [374, 375] needs to be specifically evaluated in the African context where other drivers of TB, such as HIV co-infection, are likely to be playing a much greater role than diabetes.

3.5.3 HIV factors

The prevalence of **HIV** in this cohort was particularly high at 82.9%, which is more than the reported 56% prevalence in adult patients with TB in Malawi [376]. There are a number of possible explanations for this. One consideration is that the study recruited from a large central hospital in an urban area. HIV prevalence is often higher in urban areas [377], and was double that in rural areas according to the most recent Malawi Demographic Health Survey [51]. However, HIV prevalence in patients starting TB treatment for the first time is still only approximately 65% in Blantyre (unpublished data, Prof E.L. Corbett), and patients requiring retreatment are referred to QECH from the whole of Blantyre district including both urban and rural areas, suggesting that in fact there is a true difference in HIV burden between new and retreatment patients. Given that HIV increases the risk of TB at all stages and CD4 counts [120, 378], and that a single episode of TB does not confer immunity [10], it is to be expected that HIV positive people will have more TB episodes in a lifetime than HIV negative people, particularly in areas of high TB transmission. People established on ART can live for many years, but remain at increased risk of TB throughout that time, thereby increasing their chances of having more than one episode [379, 380]. As more and more people are initiated on ART in Malawi and other African countries, a growing pool of HIV-positive people living at risk of TB for many years, and therefore at risk of recurrent episodes of TB, may develop.

TB treatment success rates are lower in people infected with HIV. This association was is also seen patients on TB retreatment, as presented in the systematic review in chapter 1 of this thesis. The increased risk of poor outcome in HIV on TB retreatment is demonstrated once again by this cohort study, in which only 66.4% of HIV positive people had successful treatment outcome, compared to 77.8% of HIV negative people. The finding that patients with CD4 count of <100 cells/mm^3 did worse than those with higher CD4 counts (55.4% success v 72.6% success; OR 2.14, 95% CI 1.01-4.53) is also in keeping with previous literature [381, 382].

The **high proportion of patients with ART failure** seen in this cohort is a major concern. HIV viral load testing was only performed once patients had been on ART for at least a year, and ART failure was defined as having an HIV viral load of >5000 copies/ml. Both of these thresholds are rather conservative (newer WHO guidelines recommend testing 6 months after initiation of ART and using a threshold of 1000 copies/ml [150]), but were chosen to be in line with local policy in order to avoid difficulties in management if patients did not meet local criteria for second line ART. Had viral load been measured after 6 months on treatment, even more ART failure may have been detected. It is possible that ART failure is common in patients on TB retreatment because this is a group in whom adherence to both ART and TB drugs is poor, putting them at risk of both ART failure and recurrent TB. Although patients with detectable HIV viral loads were given adherence counselling and referred to ART clinic for management, comprehensive assessments of ART adherence were not recorded in a systematic way as part of this study. Similarly, although only 7 (4.4%) of patients were registered as having TB treatment after default, in depth assessment of previous adherence to TB treatment was not carried out. An alternative explanation relates back once again to the issue that patients on ART for a long time will be at increased risk of developing more than one episode of TB. For many 'new' patients who have not previously been treated for TB, TB is their presenting HIV diagnosis following which they initiate ART. On the other hand, patients who have previously received TB treatment are likely to have been diagnosed with HIV during their first episode and therefore already have been on ART for some time prior to the current episode. This will result in a higher proportion of the patients on TB retreatment being at risk of ART failure. Clinical outcomes on second line ART are worse than those on first line HIV drugs [383, 384], and in the long term are likely to contribute to poor outcomes in patients with recurrent TB. In this study, only 50.0% of patients with detectable viral load successfully completed TB treatment.

3.5.4 Chronic Lung Disease

Of particular interest is the finding of an extremely high burden of chronic lung disease in patients on TB retreatment. Previous literature had gone some way to describe the features of post-tuberculous lung disease, however none has specifically assessed the burden of lung disease in patients entering TB care at the point of a recurrent episode. The key issue is that if the vast majority of patients starting TB retreatment regimen have underlying chronic lung disease, it may not be sufficient simply to treat their respiratory disease with anti-tuberculous drugs.

The commonest finding was bronchiectasis, which was present in 62/102 (60.8%) of patients who underwent CT thorax. Being HIV negative, having microbiologically confirmed TB, and a history of smoking were all independently associated with bronchiectasis. TB and smoking are well recognised risk factors for bronchiectasis [179, 385], however the association with being HIV negative requires some exploration. Bronchiectasis has been shown to be common in HIV infected children and adolescents in Sub-Saharan Africa [386], as well as in HIV infected adults in the USA [387]. However, in the case of TB associated bronchiectasis, it can be postulated that a certain degree of inflammatory response to infection is required in order to produce destructive pulmonary changes, and that HIV infected adults are less capable of mounting such an immune response. This is in keeping with the well recognised finding that HIV positive patients with TB have fewer cavitatory lesions on imaging than those who are HIV negative and are less likely to be sputum smear positive [130, 135, 137]. The finding that bronchiectasis is so prevalent in this group of patients is important because it is a diagnosis for which appropriate interventions may improve outcome. Interventions known to affect the prognosis in bronchiectasis include appropriate antibiotic management of infectious exacerbations and regular postural drainage [177, 388, 389], both of which could be easily implemented in low-resource settings. In this cohort of patients, it is possible that those with bronchiectasis were more likely to have super-added acute bacterial infection, which may contribute to more severe presentations and even explain a proportion of the hypotension seen at presentation. Further research to determine

the microbiological aetiology of infectious exacerbations of bronchiectasis in African settings would help to inform management.

Tuberculous destroyed lung results in large sections of non-functional lung parenchyma as tissue is destroyed by bronchiectasis, scaring and volume loss, and has previously been associated with poor TB outcomes. In this study, TDL was seen in 19% of patients and associated with poor outcome on univariate analysis, with successful outcome seen in only 63% of patients, compared to 84% in those without TDL. After adjustment of age, gender, smoking, HIV and confirmed TB the odds ratio for successful treatment outcome in people with TDL remained 0.32, but 95% CI was 0.09-1.13 (p-value 0.08). In fact, treatment outcomes were worse for all categories of chronic lung disease except emphysema, but once again none of these differences reached significance at a 0.05 level, possibly due to the small numbers of patients.

Emphysema was seen in 22% of patients, although only 27% of the cohort reported ever having smoked. In a setting such as Malawi, it is likely that emphysematous changes are associated with exposure to biomass fuels [390], although data about possible biomass exposure and indoor air pollution were not collected as part of this study. Many of the emphysematous changes seen were mild, which is likely to explain the relatively good outcomes in patients with radiological evidence of emphysema.

Of the 102 patients who had CT thorax performed, 77 also had spirometry after 2 months of TB treatment. Abnormal spirometry was more common in patients who had bronchiectasis (75% had abnormal spirometry compared to 55.2% without bronchiectasis) and destroyed lung (92.3% had abnormal spirometry compared to 62.5% without TDL). In practice, the greatest potential for the use of spirometry would be to screen for bronchiectasis in settings where CT thorax, which is the gold standard for diagnosis, is not routinely available. The data have already shown the weakness of plain chest X-ray in diagnosing CT confirmed bronchiectasis, and X-ray facilities are often only available at central hospitals, limiting their usefulness at

community level. If spirometry were to perform better than X-ray in predicting bronchiectasis, it may be valuable as an additional screening tool for picking up patients for whom interventions such as postural drainage might be of benefit. Using the data from this cohort study with a bronchiectasis prevalence of 60%, the positive predictive value for CT diagnosed bronchiectasis using spirometry would be 0.69, and the negative predictive value would be 0.86, suggesting it may have some use in settings where the prevalence of bronchiectasis in patients on TB retreatment was high.

As well as there being a large number of radiologically diagnosed respiratory abnormalities, pulmonary function testing also demonstrated a high level of respiratory pathology, with only 33% of patients having normal respiratory function. The high prevalence of restrictive deficit compared to obstructive defect was an unexpected finding, for which there may be several explanations. The first explanation is that there truly is a high prevalence of restrictive lung pathology, caused mostly by bronchiectasis, TDL and scarring. However, alternative explanations include secondary restriction caused by reduced lung expansion. Impaired lung expansion can be due to a number of factors such as rib cage deformity, obesity or muscle weakness [391]. In this cohort of patients with multiple acute and chronic medical problems in whom malnutrition is common, it is possible that their ability to perform spirometry was hindered by intercostal and diaphragmatic weakness. This theory is perhaps supported by the fact that restrictive pulmonary deficit was more common in those who were severely malnourished – the prevalence of restrictive deficit being 77.3%, 57.1% and 56.0% in patients with BMI <16, 16-18.4, and ≥18.5 respectively. Lastly, it must be acknowledged that, despite training and strict protocols, it is possible that the technique of patients when doing spirometry was suboptimal, as this would also result in a restrictive-looking picture. In keeping with previous literature, the progression of restrictive lung defect was variable, with the majority (57.6%) still having restriction on pulmonary function at 8 months, but others improving and a small number developing obstructive deficits.

Overall, it is clear that there is a huge burden of chronic respiratory pathology in patients with recurrent tuberculosis, a large proportion of which is directly attributable to the effects of tuberculosis on the lung. However, there are some elements which may have improved the investigation of respiratory disease in this study. Additional insights may have been gained by more longitudinal follow-up of patients. The fact that previous imaging and respiratory function testing were not available makes it hard to differentiate pulmonary disease associated with the current TB episode from disease caused by previous episodes. Similarly, although spirometry was repeated after 8 months, repeat imaging was not performed due to resource constraints. Although many findings on CT are clearly irreversible (such as scarring and large, cystic bronchiectasis) repeated measures would provide the opportunity to assess progression of disease over time. Although it was planned that all patients would have CT thorax after 2 months of treatment, due to technical problems with the CT scanner in Blantyre, patients had CT performed at different time points during treatment. This may have meant that the amount of chronic change was underestimated in those who had CT early in the course of disease, and more prevalent in those who had CT later on. Although many of the CT findings in this cohort would be consistent with chronic aspergillus infection, aspergillus serology was not performed. Further investigation of the prevalence and features of aspergillus infection in patients with recurrent TB would be an interesting area for further investigation. Additional issues which need to be explored in order to assess the impact of respiratory disease on patients with recurrent TB would involve longitudinal follow up of patients, and in particular focus on the functional and social impacts of chronic lung disease.

3.5.5 Drug toxicity

Drug toxicity was common in this cohort, and mostly caused by streptomycin. Whilst on streptomycin, 35.9% of patients developed **ototoxicity**. This is in keeping with previous literature about the incidence of aminoglycoside ototoxocity [261, 392], but it provides the largest dataset specifically concerning streptomycin, and the first from a prospective cohort of patients on streptomycin in Africa. A more

unusual finding is that the ototoxocity resolved in over half of patients at 8 months, as previous data have suggested that aminoglycoside ototoxocity is irreversible [251]. However the follow-up numbers in this study were small, and only 14 patients with ototoxicity after 2 months had repeat testing at 8 months. Risk factors for streptomycin induced ototoxicity are not well defined, although one study from South Africa has suggested that hearing loss was greater in HIV positive patients than HIV negative patients on treatment for MDR-TB [265]. In contrast, data in this study suggest that ototoxicity may be less common in HIV positive patients, with only 31.8% developing hearing loss, compared to 58.3% of HIV negative patients. The explanation for this is not obvious, but may be associated with differences in the pharmacokinetics of streptomycin, which is a question for further exploration.

The importance of ototoxicity is it's affect on peoples functional ability. Much of the ototoxocity diagnosed on formal testing was subclinical. A subgroup of 78 patients in the cohort study were also enrolled in the TB-RROC trial, in which regular screening for hearing loss using the CALFRAST test was performed (see chapter 5 [393]. Of these 78 patients, 14 had abnormal audiometry but only 1 stopped streptomycin due to presumed ototoxicity. Nevertheless, ototoxicity in this group is very common and mild hearing loss may still have subtle affects on peoples' daily activities. Therefore, if streptomycin is used as part of the Category II retreatment regimen monitoring for ototoxicity should be considered, although the optimal approach to this in poor resource settings needs to be determined.

Nephrotoxicity developed in nearly 15% of patients. This may well be an underestimate, as blood tests were not performed in a number of patients who died whilst on streptomycin, particularly those who deteriorated or died out of working hours when the study team was not available. It may also explain the lack of association between kidney injury and clinical outcome. There were no factors associated with the development of nephrotoxicity, and it is especially reassuring that patients on Tenofovir containing ART were not at greater risk of developing renal impairment whilst on streptomycin.

3.5.6 Study limitations

This study had a number of weaknesses, many of which have already been discussed whilst addressing specific aspects of the data. However, it is worth noting two overarching limitations. Firstly, the study was not powered to detect associations between treatment outcome and all of the potential risk factors. Hence, whilst it was possible to demonstrate high prevalence of co-morbidity and high incidence of toxicity, the study was frequently unable to show that these were statistically associated with poor outcome. Nevertheless, clinical issues are highlighted and it seems unlikely that such a high burden of disease is not contributing to poor outcomes in this group.

A second drawback is that the study did not recruit a control group with which to compare the prevalence of other medical conditions, for example patients receiving TB treatment for the first time or a sample from the general population. Instead, comparisons are made to published data which limits the interpretation of results. Nevertheless the complexity of medical problems in this group of patients is clearly demonstrated, and from a practical perspective, if the aim is to improve management for patients on retreatment this is not dependent on comparison with other groups.

Thirdly, a major drawback of this study is that cause of death was not determined. In determining factors which may be contributing to poor outcome, autopsy findings confirming cause of death would have been valuable information. However, it was beyond the scope of the study to perform autopsy on study participants who died for two reasons. Firstly, the local ethics board in Malawi (COMREC) at the time was not granting permission for any post-mortem examinations to be performed as part of research studies, as it was in the process of revising its policy on the matter. Secondly, discussion with other investigators at MLW suggested that previous attempts to use verbal autopsy had not been useful in this setting for determining cause of death due to difficulties in differentiation between TB and HIV related conditions (personal communication Dr P

MacPherson). The WHO Verbal autopsy tool focuses on respiratory, gastrointestinal and neurological symptoms, all of which are common in both HIV and tuberculosis, hence making the distinction very difficult [394].

Finally, there was no systematic documentation of the management of medical co-morbidity in this cohort of patients. Although the burden of co-morbidity is shown to be high, the impact of this burden is difficult to assess given the lack of autopsy data and the inability to assess the role of medical interventions applied to address the co-existing medical problems. There is little standardisation of management in Malawi for many of the co-morbid conditions seen - clinical decisions are made by a broad range of clinicians with varied levels of training and experience; and access to both diagnostic and therapeutic resources are intermittent and unpredictable. Therefore, although it would have been possible to document additional treatment received by patients in the study, the data would have been imprecise and difficult to interpret. For example, all patients underwent chest x-ray, but the clinical management of problems identified on chest x-ray such as lung abscesses, bronchiectasis or pleural disease would have been very variable, and these management decisions may have impacted clinical outcome. This is particularly important as the care received by patients in this cohort study was almost certainly enhanced by the presence of additional clinical input from members of the research team.

3.6 Conclusion

In this cohort of patients, fewer than 10% were infected with a strain of MTB which had any form of drug resistance and this was not associated with poorer outcome, yet 24% of patients died whilst on treatment. Patients who have an acute presentation with hypotension are particularly likely to do badly. The high prevalences of anaemia, HIV, ART failure and chronic lung disease are likely to contribute not only to mortality but also to morbidity in this group of patients. The additional burden of ototoxicity will further impact on the lives of patients

prescribed retreatment regimen. If clinical outcomes are to be improved for patients being treated for recurrent episodes of TB, it will be necessary to manage not only their TB disease, but also to address the entire spectrum of medical complications with which they present. The potential for interventions to reduce the impacts of co-morbidity and drug toxicity are discussed in the final chapter of the thesis.

This cohort study has described the clinical context of recurrent TB in Malawi, demonstrating that patients prescribed retreatment regimen are a complex group with multiple medical issues. It was on the background of this context that the intervention of community-based management during the intensive phase of TB retreatment was designed, piloted and evaluated.

4 Intervention pilot study

4.1 Introduction

In line with MRC guidelines, the first steps after conception of the TB-RROC intervention were to review the literature, develop theories of how the planned intervention might impact on outcomes, and engage with the Malawi NTP and other stakeholders. Following this, a pilot study was performed in order to explore the feasibility of training guardians to deliver injections.

A pilot study can be defined as a 'small study for helping to design a further confirmatory study' [395]. Pilot studies are an important preparatory stage in the development of trials, and as such form a key component of the Medical Research Council's Guidelines for Developing and Evaluating Complex Interventions [307].

There is some discrepancy regarding the differentiation between 'pilot studies' and 'feasibility studies'. Whilst some authors claim little distinction between the two [396], others describe subtle differences [397]. The National Institute for Health Research Evaluation, Trials and Studies Coordination Centre (NETSCC) defines a pilot study as:

> *"a smaller version of the main study used to test whether the components of the main study can all work together. It is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow up assessments all run smoothly'' [398];*

whereas they define a feasibility study as:

> "*a piece of research done before a main study in order to answer the question 'Can this study be done?'. It is used to estimate important parameters that are needed to design the main study. For instance standard deviation of the outcome measure, willingness of participants to be*

randomised, willingness of clinicians to recruit participants, number of eligible patients, characteristics of the proposed outcome measure, follow-up rates etc, availability of data needed or usefulness of a particular database, time needed to collect and analyse data" [398]

Many pilot studies clearly address questions of 'feasibility' and therefore the terminology is in some respects academic. As this initial study included an evaluation of the intervention proposed for the main study, the term 'pilot' has been used.

Although they can play a role in many types of study [399], pilot studies are of most relevance in the planning of a Randomised Controlled Trial (RCT). Essentially, the overall aim of a pilot study is to maximise the chances of a trial being successful, and to optimise the potential of a full scale RCT effectively and efficiently being able to answer a research question. Thabane et al [396] describe various reasons for conducting pilot studies:

- *Process:* This assesses the feasibility of the steps that need to take place as part of the main study. Examples include determining recruitment rates, retention rates etc
- *Resources:* This deals with assessing time and budget problems that can occur during the main study. The idea is to collect some pilot data on such things as the length of time to mail or fill out all the survey forms.
- *Management:* This covers potential human and data optimisation problems such as personnel and data management issues.
- *Scientific:* This deals with the assessment of treatment safety, determination of does levels and response, and estimation of treatment effect and its variance.

Pilot studies should be conducted with the same rigour as definitive trials. They should have clearly defined objectives and methodologies and be carried out according to principles of good practice. Criteria for the assessment of feasibility

should be pre-defined and clearly laid out [395, 400]. In general, pilot studies are stand-alone pieces of work separate from the main study. In certain cases, such as adaptive designs, the data obtained from a pilot can be incorporated into the main study, but caution needs to be taken as pilot data may result in the alteration of study methodology in the subsequent trial [401]. Pilot studies are not designed to test hypotheses, and do not produce data to which statistical tests of significance can be applied, rather descriptive data should be presented which directly address predefined feasibility criteria [402-404]. Likewise, sample size calculations are not a requirement of a pilot study, as these studies are not aiming to provide a definitive answer to a question of efficacy. Instead, a pilot study must recruit a sample that is representative of the target population; have eligibility criteria that are in line with those intended for the main study; and recruit a sufficient number of participants to provide the information required to address the objectives of the study [396].

The intervention that was being evaluated in this study was an entirely new approach to the delivery of long-term injectables to patients with recurrent TB in Malawi. Although community based models of care for patients on TB treatment have previously been evaluated, the idea of training guardians in Malawi to deliver injections was novel. Therefore, it was felt that an initial evaluation of the safety of the intervention was warranted prior to committing to a larger trial. Additionally, as the process of delivering care in this way had not previously been tested, a pilot study would also provide an opportunity to refine the procedures involved in the intervention. Finally, it was recognised that the main study was being run on a strictly limited budget and time scale, as it formed the basis of a PhD fellowship. Therefore it was important to establish what recruitment rates to the trial were likely to be, in order to establish whether it would be feasible to conduct the definitive RCT within the resource constraints.

4.2 Aims and objectives

The overall aim of this pilot study was to provide information that would be used to inform the design of a randomised controlled trial planned to evaluate a community based model of care during the intensive phase of TB retreatment.

The main research question was:

Is it feasible to train guardians to deliver streptomycin to patients in the community during the intensive phase of the tuberculosis retreatment regimen?

In line with the classification proposed by Thabane et al, the specific objectives of this pilot study were:

1. To assess the feasibility of training guardians to administer intramuscular streptomycin *(Process and scientific).*

2. To identify obstacles in the training of guardians in the technique of intramuscular injection, in order to optimise the training procedures prior to commencing the main study *(Resources).*

3. To trial data collection and management tools in order to optimise procedures prior to commencing the main study *(Management).*

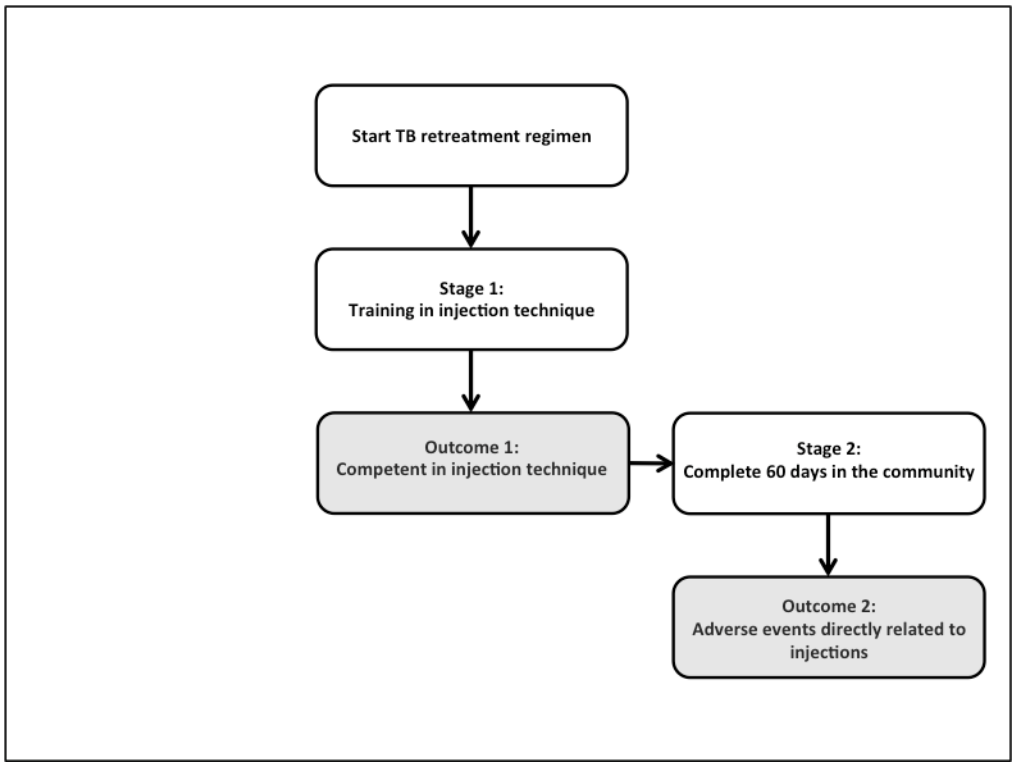
These objectives were designed in order to determine whether the intervention was safe, whether the planned study was feasible within the constraints of available resources and likely rates of recruitment, and to optimise the processes and management of the main study.

4.3 Methods

4.3.1 Study design

A pilot study was performed in which a small cohort of patients was prospectively recruited and managed as per the intervention planned for the main trial. It was planned that all patients starting retreatment regimen for tuberculosis at QECH during a one-month period were screened for eligibility. In stage 1 of the study, the guardians of all those who enrolled were trained in the technique of intramuscular injection. In stage 2, a consecutive subgroup of those who successfully completed the training were discharged and managed in the community (figure 26). There was no randomisation process. Patients in the community were followed up until completion of the intensive phase of treatment. Eligibility criteria, follow up procedures and data management procedures were in line with those planned for the main study.

Figure 26. Pilot study flow diagram



4.3.2 Outcome measures

Outcome measures were designed to determine the feasibility of the planned intervention.

The primary outcome measure was:

> *The proportion of patients managed in the community who developed serious adverse events as a direct complication of the intramuscular administration of streptomycin.*

'Serious adverse events as a direct complication of the intramuscular administration of streptomycin' were defined as:

- Deep soft tissue infection at an injection site, or
- Sciatic nerve palsy

These are well known but uncommon complications of intramuscular injection. For the purposes of this study, a deep soft tissue infection was defined as an infection at an injection site that required surgical drainage or intravenous antibiotic therapy. Sciatic nerve palsy was determined by examination for unilateral sensory loss in the distribution of enervation by the sciatic nerve (below the knee), or unilateral weakness of the lower leg, particularly foot drop.

It is worth noting that the primary outcome in this pilot study was not the same as that planned for the main trial. The primary outcome in the main trial was 'still alive and on treatment at the end of the intervention'. However, the proportion of patients predicted to be 'still alive and on treatment' at 2 months was 87% (based on unpublished data from the TB register at QECH). Therefore, in a small pilot study the uncertainty around the estimate would be too large to be able to make an assessment of feasibility [405]. Rather, it was felt that a direct assessment of

guardians' ability to deliver injections without complication would be of more value in determining whether the intervention was safe.

The secondary outcome measure was:

> *The proportion of patients starting retreatment regimen whose guardians reach competency in the technique of intramuscular injection following training.*

Competency was assessed using a standard proforma consisting of 10 specific tasks (appendix 3). Guardians were required to complete all 10 steps correctly in order to be considered competent to safely perform the procedure of intramuscular injection.

It was judged that the main study would be feasible if:

> No more than one patient managed in the community developed a serious adverse event as a direct complication of the intramuscular administration of streptomycin.
>
> AND
>
> ≥65% of the guardians of patients starting retreatment regimen reached competency in the technique of intramuscular injection following training.

The baseline rates of these complications were unknown. There are no published data that prospectively describe the incidence of either sciatic nerve palsy or abscess following intramuscular injection in Malawi or a similar setting. However, considering these are complications that are well known to arise from the procedure in a broad range of situations [406-408], it was reasonable to expect there might have been a small number of events during the course of the study. A

very conservative feasibility threshold for adverse events in the pilot study was chosen in order to emphasise and ensure patient safety.

Recruitment to the main trial was intended to run for 18 – 20 months. Given that approximately 20-25 patients per month register for TB retreatment at each of QECH and Bwaila Hospital, it was estimated that in order to reach the target sample size in the main trial, at least 65% of all guardians of patients who were screened would have to reach competency in the technique of intramuscular injection.

4.3.3 Sample size

No formal sample size calculation was undertaken as this was a pilot study [400]. Rather, the number of participants was determined by deciding on a minimum number that would be required to provide sufficient data to optimize the processes in the planned trial. On average during a one-month period in 2010, 26 patients were started on retreatment regimen at QECH (data from Malawi NTP records). It was believed that by recruiting participants during a one-month period, the data from training 20-30 guardians in injection technique and following up a subgroup of 10 patients in the community would generate enough information that could be used to help optimise the main study. The pilot was designed to ensure that the sample recruited would be representative of the sample recruited to the main trial.

4.3.4 Eligibility

It was anticipated that the main study would be run as a pragmatic trial (see chapter 2) [315], and as such all patients eligible for retreatment regimen according to Malawi NTP guidelines would be eligible for initial entry [61]. The pilot study was therefore designed to be consistent with this approach and aimed to reflect the situation in both the planned trial and routine practice in Malawi. Eligibility criteria were defined as follows:

Inclusion criteria

- Adults >16 years starting TB retreatment regimen
- Able to give informed consent
- Able to identify a suitable guardian

Exclusion criteria

- Patients identified as having MDR-TB on phenotypic drug sensitivity testing, or being treated for MDR-TB on the basis of Rifampicin resistance detected using GXP (Patients in whom MDR-TB is diagnosed were referred to the NTP MDR programme).
- Pregnant women
- Unable to give informed consent
- Unable to identify a suitable guardian

4.3.5 Data collection process

There was a 2-stage enrolment and recruitment process. In the first stage, all patients starting retreatment regimen were approached to identify a guardian willing to participate in the study. The guardian was then trained in the technique of intramuscular injection. In the second stage, only a subgroup of those who were deemed clinically fit for discharge *and* whose guardian became competent at injection technique were discharged from the hospital in order to complete the intensive phase of treatment in the community.

4.3.5.1 Recruitment: stage 1

Patients starting retreatment regime were identified each weekday by reviewing the TB register and TB ward register at QECH. All eligible patients were approached

to take part in the study, and those who agreed were asked to identify a guardian. Initial consent to participate in this phase of the study was obtained separately from both the patient and the guardian. Logs were kept of all patients screened and all participants enrolled into stage 1. Baseline demographic, socio-economic and clinical data were collected on a standard Case Record Form (CRF). Whilst the patient was admitted to the ward, the guardian was trained in the technique of intramuscular injection. During the training period, a small reimbursement for transport was available to guardians, based on standard costs of transport depending on the distance they lived from the hospital. The study nurse instructed guardians daily during weekdays on a one-to-one basis. Once the study nurse believed that a guardian was capable of performing the injection using the correct technique, the guardian underwent a structured competency assessment (appendix 3). The competency assessment was devised by carefully breaking down the components involved in performing intramuscular injection. Discussion amongst the study team and ward nurses identified the crucial steps involved in administering injections. This process was aided watching training videos and by the development and piloting of the pictorial instruction card (appendix 4). Once the essential steps had been established, the assessment form was developed.

Following the competency assessment, patients continued to receive routine clinical care under their admitting medical team and had no further involvement in the study unless enrolled into stage 2. These participants formed the cohort for analysis of the secondary outcome (the proportion of guardians successfully trained in injection technique).

4.3.5.2 Recruitment: stage 2

It was planned that the first 10 patients who were clinically fit for discharge *and* whose guardians passed the competency assessment would be discharged from hospital in order to complete the intensive phase of TB retreatment at home, including daily streptomycin being delivered by their guardian. Prior to discharge, additional consent to participate in the second stage of the study was obtained. A

log was kept of all patients participating in the second stage of the pilot study. These patients formed the cohort for analysis of the primary outcome.

4.3.5.3 Follow up

Follow up procedures for those enrolled into stage 2 of the study were in line with those described in detail for the main trial (Chapter 5). Briefly, routine follow up was conduced at weeks 1, 3, 5, and 7 post discharge from the ward. Participants were also able to contact the study team at any time if they had concerns. These events were recorded as unplanned follow up and logged as adverse events. All patients were reviewed at the end of the intervention i.e. at completion of the 2-month intensive phase of retreatment. Following completion of the intervention, patients re-entered routine TB clinical care provided at QECH or their local TB registration centre.

4.3.5.4 Adverse event monitoring and reporting

Adverse events, serious adverse events and unexpected serious adverse events were defined as per the protocol in the main trial (see chapter 5). For the duration of the pilot study, all adverse events were reported immediately to the PI. The PI and study nurse jointly reviewed all patients experiencing adverse events, and completed an adverse event form for each episode. Considering the small number of participants in the pilot study, adverse events were compiled and reported at the end of the study period.

4.3.5.5 Statistical methods

This was a pilot study involving a small number of participants and was not designed to produce data for the statistical analysis of effect. Rather, the proportion of guardians reaching competency and the number of serious adverse events were reported in order to determine whether the pre-established feasibility criteria were met.

4.4 Results

The study recruited participants from 9th January 2013 – 13 March 2013. A total of 24 patients starting retreatment regimen were screened (figure 27).

4.4.1 Primary outcome: Adverse events

Ten patients and their guardians were enrolled into stage 2 of the study, discharged from hospital and completed the intensive phase of TB retreatment at home. The characteristics of the patients and guardians are shown in table 29. There were no serious adverse events directly related to the administration of intramuscular streptomycin in those patients discharged to the community.

One patient died on day 60 of treatment. She was a 28 year old HIV positive woman being treated for presumed extra-pulmonary TB. Following discharge to the community, she had been readmitted to hospital with fever, anaemia and splenomegaly. No definitive diagnosis was made but she initially responded to empirical treatment for a presumed episode of bacterial sepsis and was discharged back to the community. She later died at home on the last day of her course of streptomycin, after a further short febrile illness of undetermined aetiology. The guardian did not report any symptoms suggestive of intramuscular abscess or sciatic nerve injury.

4.4.2 Secondary outcome: Proportion of guardians trained to inject

There were 19 participants enrolled into stage 1 of the study. Seventeen guardians who began training successfully completed training and passed the competency assessment. The median time taken by guardians to reach competency was 3 days (range 2 – 10 days). Given that 24 patients were screened for eligibility into the study, the overall proportion of guardians who reached competency was 70.1%.

Figure 27. Participant recruitment to Pilot Study

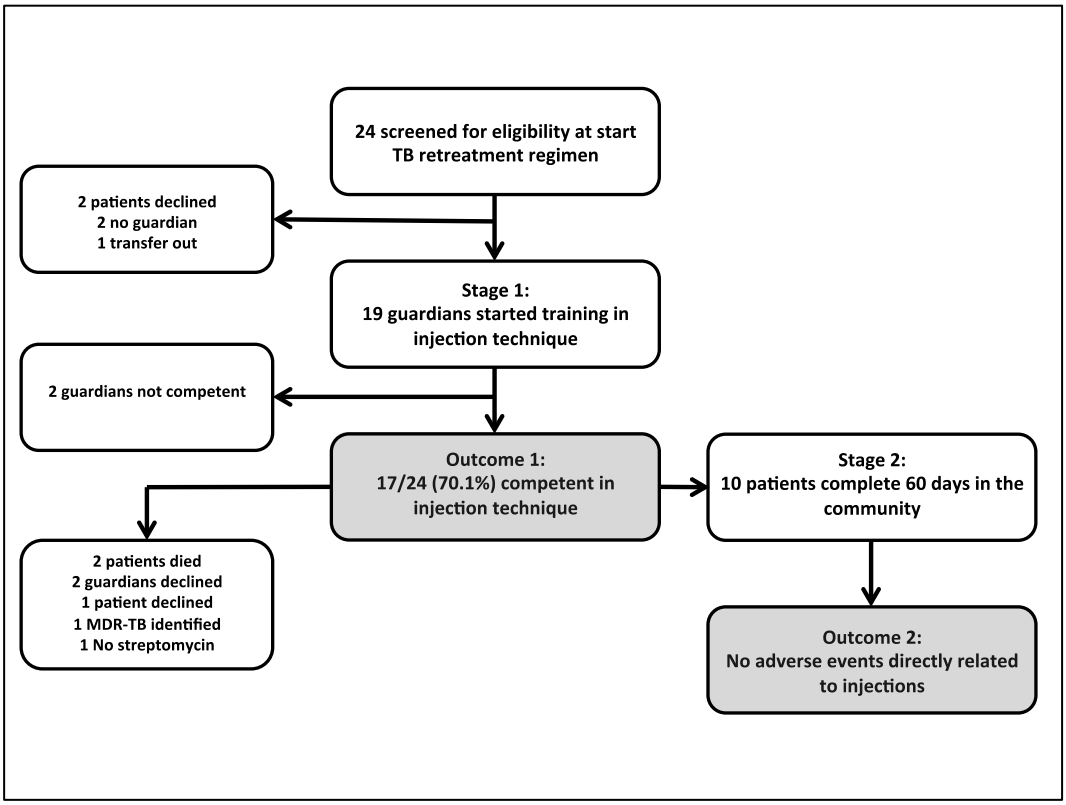


Table 29. Characteristics of participants enrolled into the TB-RROC pilot study

Characteristic	n
Patient characteristics	
Age (mean, yrs)	36.1
Sex	
Male	6
Female	4
TB classification	
Pulmonary	8
Extra-Pulmonary	2
TB category	
Relapse	6
TAD	0
Fail	0
Other	4
Number of previous TB episodes	
1	9
2	1
HIV status	
Positive	8
Negative	2
ART status amongst HIV+	
On ART	7
Not on ART	1
Guardian Characteristics	
Age (mean, yrs)	37.0
Sex	
Male	4
Female	6
Relationship to patient	
Spouse	4
Sibling	2
Parent	1
Aunt/Uncle	2
Niece/Nephew	1
Occupation	
Paid employee	4
Self-employed	4
Unemployed	2

4.5 Discussion

4.5.1 Feasibility

There were no serious adverse events as a direct complication of intramuscular injection, and more than 65% of guardians were successfully trained to administer intramuscular streptomycin. As both feasibility criteria were met, it was concluded that a larger trial would be feasible.

There was one serious adverse event - the death of a patient on day 60 of treatment. The case was reviewed and it was concluded that the event did not occur as a result of the intervention. There was no suggestion that her illness was caused by a direct complication of having received injections from the guardian. The intercurrent, recurring episodes suggest a possible additional underlying pathology. Although she eventually died in the community, she had had a previous readmission to hospital from which she recovered sufficiently to be discharged home. Mortality in this group of patients is known to be high, with 11% of patients at QECH in 2011 dying within the first 2 months of TB retreatment (unpublished data from QECH TB register). Therefore, 1 death amongst 10 patients managed in the community was within the expected mortality and not thought to be a contraindication to proceed to the main trial.

Recruitment to the pilot study was considerably slower than anticipated. In order to enrol 10 patients into stage 2 of the study, recruitment had to be extended beyond the planned one month, so that the recruitment period ran from 9th January to 13th March 2013.

The pilot was seriously affected by an interruption in the supply of streptomycin, which occurred countrywide during the first three months of 2013. This had major implications for both recruitment and retention of participants. Of greatest significance was the fact that only 24 patients were screened during a period of more than 2 months. This is in contrast to the mean number of patients registering

for TB retreatment at QECH in 2011, which was 26 per month. From observation and discussion with health care providers, it was evident during this period that fewer patients were being referred to QECH for TB retreatment. This was likely to be because it was known amongst those working at TB registration centres across the region that streptomycin was not available at the central hospital. Additionally, some patients and guardians on the ward who may otherwise have participated in the study were unable or unwilling to participate. There were a number of occasions where training was interrupted and participants became frustrated and withdrew from the study, or where guardians were competent to do injections but there was not sufficient stock of streptomycin to be able to discharge patients with an adequate supply. Of the 17 guardians who became competent in injection technique, 7 did not enter stage 2 of the study. Of these, 4 were not discharged due to reasons directly related to the inconsistent supply of streptomycin: 2 guardians withdrew, 1 patient withdrew, and in 1 case although both were still willing to participate there was insufficient supply of streptomycin.

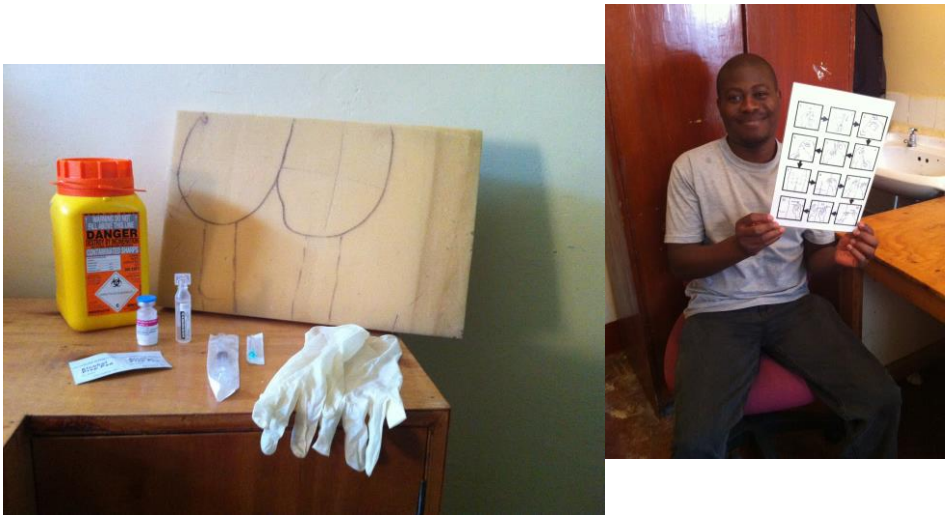
The lack of streptomycin was an unprecedented event, with supplies of TB drugs in Malawi having been consistent for many years [409]. The exact reasons for the interruption in supply remain unclear but are likely to be multifactorial. It was thought that although unlikely to happen again, the possibility of further interruptions in drug supply, which would hinder the trial, needed to be considered. Key components of the World Health Organisation's Stop TB Strategy are that governments should provide a standardised treatment TB regimen and ensure effective drug supply and management systems for TB [65]. So, whilst the possibility of the study procuring streptomycin to be used in emergency situations was debated, it was decided that this should only be considered as a last resort. Strategies whereby the study could support the sourcing of drugs through local systems (for example assisting with transport to collect streptomycin from other Ministry of Health facilities in the region) were considered as preferable alternatives.

4.5.2 Training technique

The processes by which guardians were taught to administer intramuscular injections were optimised. Tools devised included (see figure 28):

- Foam pads were designed for use when practicing injection technique.
- Illustrated instruction cards were developed (appendix 4).
- DOT cards for participants to complete whilst receiving treatment in the community were optimised (appendix 5). Dates of upcoming visits and study team contact details were added to the original design of these cards.

Figure 28. Materials developed for training guardians to deliver streptomycin injections



In addition to improving the one-to-one training delivered to guardians, the pilot study provided an opportunity to sensitise staff on the TB ward to the study. Clinicians, nurses and TB officers were made aware of the study and became familiar with the processes involved in recruiting and training participants.

4.5.3 Data collection and management

Data were collected using paper CRFs and captured using Teleform scanning software. A number of changes were made to the data management procedures, including:

- In addition to variable names, each variable was given a unique letter and number linking it to the form and the position on the form on which it could be found.
- Questions to which there could be more than one response were not captured accurately by the Teleform system during the pilot. Adjustments were made so that each answer was entered into the database as a separate variable.
- Barcodes were found not to be useful. They did not scan well into the system and as there was no parallel recruitment (only one study nurse enrolling at each site at any one time) they were not thought to be necessary. The participant study number on each page was found to be sufficient.
- During the pilot study participants were allocated both a screening number and an enrolment number, which resulted in confusion on a number of occasions. It was also recognised that there was potential for further complication during the main study as patients were going to be screened for entry into a cohort study as well as the trial and would be enrolled into one, both or neither of the studies. Therefore it was decided to allocate one study identification number to each participant, which would remain their unique identifier throughout the screening, enrolment and follow up processes, hence simplifying the system.

Following presentation of the pilot data to research colleagues, an additional variable was added which captured the education level obtained by the guardians who were trained. Questions were asked about guardian's occupation during the pilot study. However, one of the concerns about this intervention had been

whether guardians who were illiterate would be able to learn to deliver injections. Asking guardians about their educational attainment better captured this information.

A number of issues that were discussed with patients during the process of data collection were of a potentially sensitive nature. Furthermore, the questions asked in one questionnaire had the potential to affect answers to questions subsequently asked in another questionnaire. For example, asking a patient about whether they had had thoughts of suicide and feelings of worthlessness (as part of the SRQ screening for depression) may have affected the answers they then provided for the EQ-5D quality of life measurement. It was therefore established that during enrolment to the study the questionnaires should be administered in the following order:

1. Baseline clinical data
2. Demographic information
3. EQ-5D quality of life assessment
4. SRQ

All amendments to training and data collection procedures were incorporated into the protocol and standard operating procedures for the main trial.

4.6 Conclusions

In summary, this pilot study demonstrated that progression to a larger randomised trial was justified, as both predefined feasibility criteria were met – there were no complications as a direct result of guardians administering streptomycin in the 10 patients discharged to the community, and more than 65% of those screened had a guardian who successfully learnt to administer intramuscular injections. The study also provided the opportunity to improve data management systems and optimise the procedures involved in the planned intervention.

5 The TB-RROC Trial

5.1 Introduction

Having established in a pilot study that it was feasible to train guardians to deliver streptomycin in the community, a definitive trial of the intervention was conducted. This, the first component of a multi-method evaluation of the TB-RROC intervention, primarily aimed to assess clinical outcomes. A pragmatic, individually randomised trial of hospital versus community-based management during the intensive phase of TB retreatment was performed.

5.2 Aims and objectives

The overall aim of this study was to determine the optimal setting for the delivery of streptomycin during the intensive phase of TB retreatment regimen in Malawi.

The specific objective was to assess the feasibility and safety of training guardians to administer streptomycin to patients at home during the intensive phase of TB retreatment regimen.

5.3 Methods

5.3.1 Study design

The study was an individually randomised controlled clinical trial conducted across two sites in Malawi – Queen Elizabeth Central Hospital in Blantyre and Bwaila Hospital in Lilongwe. In order to maximise the usefulness of the data to policy makers in Malawi, the trial adopted a pragmatic design in which operational conditions were replicated as far as possible. It aimed to detect non-inferiority in the intervention arm as it was believed that if clinical outcomes were shown to be *no worse* in patients managed at home, and the intervention demonstrated potential social and economic *benefits*, the recommendation would be to adopt the new method of care delivery. The primary outcome of the trial was 'still alive and on treatment at the end of 2 months of TB treatment.' The study employed a 2-

stage enrolment and randomisation process: patients starting retreatment regimen were screened for eligibility, and asked to identify a guardian. Only once guardians were trained in injection technique and patients fit for discharge were participants randomised and formally enrolled in the trial.

5.3.2 Outcome measures

The primary outcome was:

"Successful treatment at the end of the 2 month intervention period"

The definition of successful treatment was adapted from the WHO and Malawi NTP operational reporting guidelines, which state that successful treatment includes patients who have been cured and those who have completed treatment [61, 66]. Unsuccessful treatment includes all patients who have died, defaulted or whose outcome is unknown. For the purpose of this study successful treatment included all those *"still alive and on treatment at the time of assessment after 2 months treatment."* A primary outcome at two months was chosen because it was believed that the potential for impact would be greatest during the period during which patients were actually receiving intramuscular injections as part of the intervention. Additionally, although it is recognised that end of treatment (8 month) outcomes are of primary importance in tuberculosis control, the project was confined by the timeline of the PhD fellowship, which was too short to allow an additional six months of follow up.

Secondary outcomes were:

- 2-month culture conversion in those culture positive at baseline
- 8-month programmatic TB outcome
- Serious Adverse Events during the intensive phase of treatment
- Karnofsky score at 2 months
- Mental Health status at 2 months

5.3.3 Eligibility

Inclusion criteria

- Adults ≥ 16 years of age starting TB retreatment regimen
- Patients able to give informed consent
- Patients able to identify a suitable treatment supporter

Exclusion criteria

- Patients identified as having MDR-TB on phenotypic drug sensitivity testing, or being treated for MDR-TB on the basis of Rifampicin resistance detected using GXP (these patients were referred to the NTP MDR treatment programme)
- Pregnant women
- Patients not planning to stay in Blantyre/Lilongwe for the 2-month duration of the intervention
- Patients unable to give informed consent
- Patients unable to identify a suitable guardian

5.3.4 Study procedures

5.3.4.1 Initial screening and enrolment

Patients starting retreatment regimen were identified each weekday by reviewing the TB and ward registers at each site. All eligible patients starting retreatment regimen were approached to take part in the study, and those who agreed were asked to identify a guardian for training. Consent to participate in this phase of the study was obtained from both patients and their guardians. Logs were kept of all patients screened and all patients enrolled into the first stage of the study. Baseline demographic, socio-economic and clinical data were collected on a standard Case Record Form (CRF). Mental health status was assessed at baseline and again at the end of the intervention using a Chichewa validated self-reporting questionnaire (SRQ). This tool was developed by the WHO to be used in screening for common

mental disorder, and consists of 20 questions which explore symptoms of depression and anxiety [410]. Patients scoring 8/20 or higher were classified as having common mental disorder [411].

5.3.4.2 Training guardians

Whilst patients were admitted to the ward, the study nurse trained recruited guardians in the technique of intramuscular injection. This involved daily instruction and supervision, and included training in all aspects of streptomycin administration including injection procedure, sterile technique and safe disposal of sharps. Once it was thought that the guardian was able to safely perform the injection, they underwent a structured competency assessment. Guardians were given three attempts to pass the competency assessment. Whilst on the ward, all other aspects of TB care remained unchanged. All patients were offered HIV counselling and testing, and were referred to Antiretroviral Therapy (ART) clinic as appropriate.

5.3.4.3 Randomisation

Participants were randomised to receive hospital or community based care once the guardian had passed the competency assessment and the patient was declared fit for discharge by a clinician. Randomisation was carried out by the data team at MLW who were not involved in the conduct of the trial in any other form. Block randomisation using variable block sizes of 4 or 6 was performed using a computer random number generator to produce an equal allocation ratio. Allocation concealment was ensured by using sequentially numbered opaque sealed envelopes that were prepared by an independent person and opened only after participant details had been written on the envelope. Given the nature of the intervention, there was no blinding.

5.3.4.4 Follow up of study participants

Patients were reviewed either at home or on the ward 1, 3, 5 and 7 weeks post randomisation. Reviews were conducted by the study fieldworker. At each review the following took place:

- Assessment for adverse events, including:
  - Assessment of hearing using CALFRAST test [2]
  - Assessment of urine output, by enquiring if the patient had passed urine during the previous 24 hours
  - Assessment for sciatic nerve injury, by asking the patient about unilateral leg weakness or numbness
  - Assessment of the injection site, by asking about symptoms and examination for swelling, redness and discharge
  - Documentation of any medications prescribed by a clinician in the intervening period since the last review
- Documentation of Karnofsky score

For patients managed in the community, the following also took place at each visit:

- Collection of all used equipment
- Delivery of all equipment required for the next two weeks of treatment, including needles, syringes, gloves, sharps disposal boxes, drug vials and water for injection
- Adherence assessment by self-report and 'vial count' (equivalent to 'pill count' employed as a standard means of assessment of adherence to ART)
- At the first visit, injection technique was also assessed to ensure competence was maintained in the home environment

[2] The *'calibrated finger rub auditory screening test' (CALFRAST)* has been validated in the USA as a routine diagnostic screening tool for hearing loss. It involves the examiner holding their arms out to either side of the patient's head; rubbing the fingers strongly on one side; and asking the patient which side they hear a sound. This is repeated 3 times. If the patient is able to hear a strong finger rub, the procedure is repeated using a faint finger rub. 393. Torres-Russotto, D., et al., *Calibrated finger rub auditory screening test (CALFRAST).* Neurology, 2009. **72**(18): p. 1595-600.

5.3.4.5 Unplanned follow up

If participants encountered problems between routine visits there were clear procedures by which they could contact the study team. Patients and guardians were given a telephone number to call the study team and if necessary, a visit to the patient or review at the health facility was arranged. Adverse events were recorded on a standard proforma (appendix 6).

5.3.4.6 Withdrawal from the intervention

Readmission to the TB ward was arranged immediately for any patient in the community who, at any point during follow up was deemed unable to safely continue participating in the intervention for any reason, including:

- Inability to continue administration of TB treatment e.g. if trained guardian was no longer available
- Any illness requiring admission to hospital
- Patient or guardian's unwillingness to continue in the study

In a situation where a patient was admitted for management of an acute clinical event from which they fully recovered, they were able to return home and continue to receive injections delivered by their guardian if it was clinically appropriate to do so. If the guardian was unable to continue safely administering injections (including direct complication as a result of the injection i.e. abscess at an injection site or sciatic nerve injury), the patient would have been withdrawn permanently from the intervention and completed their course of streptomycin in hospital.

5.3.4.7 Completion

All patients were reviewed at the end of the intervention period i.e. at completion of the 2-month intensive phase of treatment. Clinical and socio-economic data were captured using standard CRFs. Following the completion of the intervention,

patients re-entered routine TB care under the NTP and completed treatment on an outpatient basis as per standard practice. Final outcomes were recorded from the TB register after patients had completed the 8 month course of retreatment.

5.3.5 Adverse events monitoring

As the trial was designed pragmatically in order to provide appropriate, meaningful data for making policy decisions about scale up of the intervention in Malawi, there was an emphasis on maintaining a research environment as representative of the 'real-life' situation in Malawi as possible. The adverse event monitoring in this study therefore aimed to be a realistic reflection of standard practice within the routine health-care system, whilst maintaining patient safety as a priority at all times.

5.3.5.1 Definitions

In order to reflect the particular situation of a community based intervention in which adverse event monitoring is necessarily different from monitoring in a therapeutic drug trial, definitions of adverse events were adapted from standard definitions [412] (table 30).

5.3.5.2 Identification and management of adverse events

There were three methods by which adverse events could be identified. Firstly, during a routine follow up visit; secondly by a participant contacting the study team between scheduled reviews; and lastly if a participant failed to attend a routine review. Patients presenting with clinical adverse events were reviewed by the study PI or another nominated clinician. Blood-borne virus exposures were managed by the study team according to Malawi Ministry of Health guidelines, including providing post-exposure prophylaxis for HIV if necessary, and recorded as an SAE. If a patient missed more than 2 doses of TB treatment between routine review visits, an adherence adverse event was recorded. Adherence counselling was provided and the participants were reviewed after one week. At the one-week follow up visit, if the patient had missed more than one dose, they were readmitted to the TB ward

for completion of the intensive phase of treatment (therefore constituting an SAE). If participants did not attend a scheduled routine follow up visit, all attempts were made to contact them by telephone and community visits. If a successful follow up visit was not completed within 2 weeks of the missed appointment, this constituted a default event which was automatically classified as an SAE. All adverse events were reviewed and recorded by the study clinician at each site.

Table 30. Definitions of adverse events

Adverse event (AE)	Any untoward medical occurrence in a study participant
Clinical event	Any illness or clinical injury, including possible infection at an injection site, possible sciatic nerve injury, possible renal impairment, possible hearing loss, prescription of any new medication
PEP event	Any possible blood-borne infection exposure occurring in relation to administration of streptomycin, including needle-stick injuries, which may or may not require post exposure prophylaxis (PEP) for HIV
Adherence event	Any situation in which the guardian does not administer daily streptomycin injections, and includes missed doses identified by self-report or vial count at routine review, or the guardian being unavailable to give the dose for any other reason (e.g. travelling away)
Default event	Any missed routine follow up visit
Serious Adverse Event (SAE)	Any adverse event that: i. Results in death ii. Is life-threatening iii. Requires hospitalisation or prolongation of existing hospitalisation (including readmission because of any clinical, adherence, safety or PEP event) iv. Results in persistent or significant disability or incapacity (including sciatic nerve injury or ototoxicity) v. Results in a patient being lost to follow up vi. Results in any caregiver requiring Post Exposure Prophylaxis following possible exposure to blood-borne virus
Unexpected Serious Adverse Event (USAE)	Any SAE that, for any reason, is deemed to be unexpected and requires expedited review

5.3.6 Study oversight, monitoring and administration

5.3.6.1 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) was established which consisted of three independent people, all of whom were senior academics with experience of research in Malawi (Prof Neil French (Chair), Prof Stephen Gordon, Dr Mas Chaponda). Considering the trial did not involve an investigational medical product in terms of usage, dose or indication, an appropriate reporting mechanism was devised. Rather than determining rates and features of adverse reactions due to a study drug, the aim of this reporting mechanism was to ensure safety of the new method of delivering care. Reporting therefore focussed on monthly rates of SAEs, particularly those that could be associated with the incorrect delivery of intramuscular injections by guardians in the community i.e. sciatic nerve palsy and abscess at the site of intramuscular injection. Reports of all SAEs were compiled and sent to the sponsor and DSMB each month . Any Unexpected Serious Adverse Event were reported through an expedited reporting mechanism within 48 hours.

The primary concern regarding community based management was the possibility of unsafe delivery of intramuscular injections by guardians i.e. incorrect technique which resulted in intramuscular abscess or sciatic nerve palsy. There were no prospective data on which to base any planned evaluation, and events were likely to be rare. Therefore, in conjunction with the DSMB, a 'halting rule' was devised which would trigger a review of procedures should there be an excess of absolute numbers of complications in the community group. It was planned that if the combined number of sciatic nerve palsies and abscesses in the home group exceeded the number in the hospital group by more than 3, recruitment to the study would be halted, pending review by the DSMB and TSC who would advise whether there were any steps which could be put into place to avoid further incidents, or whether the study should be stopped (see appendix 7 for DSMB terms of reference and interim monitoring report).

5.3.6.2 Trial Steering Committee

A Trial Steering Committee (TSC) consisting of an independent chair experienced in running clinical trials in Malawi (Dr Kamija Phiri); two independent Malawi-based clinical researchers (Prof. Malcolm Molyneux, and Prof Henry Mwandumba) and a representative from the Malawi NTP (Mr Kruger Kaswaswa) was established to provide independent advice and monitoring.

5.3.6.3 Monitoring and Audit

External audits were carried out by the Research Support Centre at the Malawi College of Medicine at both study sites. The first audits were during the first six months of recruitment at each site, and subsequent audits were conducted annually during the remainder of the study period. The PI was responsible for ensuring that problem areas identified during the audits were rectified and for circulating details of actions taken to the TSC.

5.3.6.4 Community Advisory Board

A Community Advisory Board (CAB) was established in Blantyre which consisted of 6 members including a patient who had recently received TB retreatment and the guardian of a patient on TB retreatment, as well as health workers involved in TB care and lay community members. The members of the CAB were identified through personal contacts at QECH and by the Science and Communications officers at MLW who had experience of running an established CAB within the organisation and who were involved in a large community-based TB intervention in Blantyre. The CAB met once prior to submission of the protocol to the ethical committees; once following completion of the pilot study but before the start of the main trial; and once towards the end of the study.

5.3.7 Sample size

It was assumed that 87% of patients managed in hospital would still be alive and on treatment at the end of the 60 day intervention period[3]. It was also assumed that the rate of successful outcome would be slightly, but not meaningfully, lower in the intervention group and therefore that the proportion being still alive and on treatment at 60 days would be 82% in the intervention group. The sample size was calculated based on a non-inferiority margin of 6%. This margin was chosen because a 6% change in outcome was judged not to be clinically meaningful, and because it is less than half the estimated rate of unsuccessful outcome (13%) from previous data. Using a one-sided alpha at a level of 0.05, in order to achieve a power of 80%, it was calculated that a sample size of 268 would be required.

5.3.8 Statistical analysis

The primary analysis performed was based on Intention to Treat. In this strategy participants were included in the analyses according to the arm that they were randomised to, irrespective of the actual intervention received. If participants were randomised in error without having met the criteria for randomisation (the guardian being competent to administer streptomycin and the patient being declared fit for discharge by a clinician), they were not included in the analysis but reported as protocol deviations. Secondary Per Protocol analysis was planned as a sensitivity analysis, and for this purpose a protocol deviation was defined as any participant who was randomised to community management but was not discharged from hospital by the time they completed 60 days of streptomycin. Any readmissions to hospital did not constitute protocol deviations, as admission to hospital may form part of the intervention. Likewise, incorrect administration of streptomycin was not considered a protocol deviation, but instead defined as an adverse event.

[3] An unpublished evaluation of TB records at QECH in 2012 demonstrated that 87% of patients started on retreatment regimen were still alive and on treatment after 2 months.

A single planned interim analysis was conduced after 130 (approximately half of the study participants) had been recruited. Based on a binomial probability with an expected probability of 10%, it was stated the trial would stopped if the p-value for difference in mortality between the hospital and community groups was less than 0.01.

Efficacy outcomes are presented as proportions and compared using the Fishers exact test for the comparison of two proportions. The risk difference for unsuccessful treatment outcome was estimated with 95% confidence intervals. Risk ratios with 95% confidence intervals for key 2-month outcomes (death, default and culture conversion) and detailed 8-month outcomes were calculated. The median Karnofsky scores and IQRs at the end of the intervention was estimated for each group. There were no planned subgroup analyses.

5.4 Results

5.4.1 Study participants

Between June 2013 and February 2015, 456 patients starting TB retreatment regimen were screened. Of those screened, 278 had guardians who began training to administer streptomycin. After further withdrawals during the period of training, a total of 204 participants were randomised – 103 to the intervention arm and 101 to receive standard of care (figure 29). One patient was randomised in error prior to being declared fit for discharge by a clinician. Of the 204 participants randomised, 144 were enrolled in Blantyre and the remaining 60 in Lilongwe. Of the 144 patients enrolled into the trial in Blantyre, 78 also participated in the cohort study.

A meeting of the Trial Steering Committee was held in February 2015, at which it was decided to stop recruitment of the trial early due to futility. At the time of the meeting, 200 patients had been recruited. The event rate in the trial was much lower than the 0.13 which had been projected - 0.0645 in the intervention arm and 0.0426 in the control arm (risk difference -0.0219). Assuming that the proportion of

success remained the same in both arms, it was projected that in order to establish a risk difference with 95% confidence intervals which were within the -0.06 non-inferiority margin, recruitment would need to continue until at least 600 participants had been recruited (figure 30), and that this was not feasible given the resources available.

Figure 29. Trial recruitment

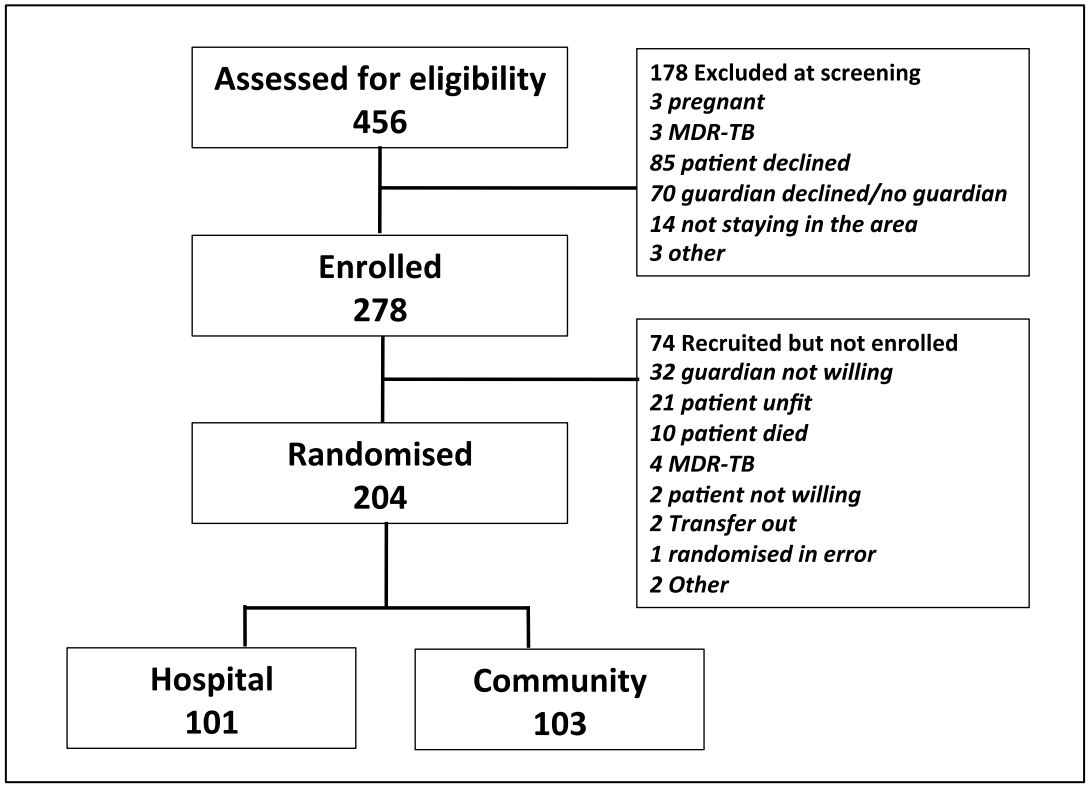
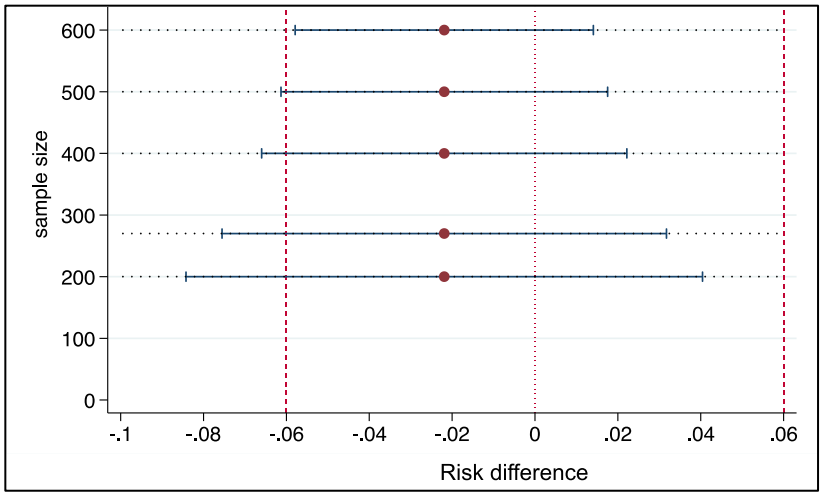


Figure 30. Risk difference with 95% confidence intervals at different sample sizes



Characteristics of the study participants are summarised in table 31. Overall, the median age of patients was 36.5 years (IQR 30.0 - 44.0 years), and 69.6% were male. The majority of patients (89.2%) had pulmonary TB, which was classified most commonly as relapse (48.5%) or 'other' (41.7%). The HIV prevalence was 80.4% (median CD4 count 177 (IQR 82-423) cells/mm^3), of whom 131 (80.9%) were on ART prior to starting TB retreatment. The proportion of patients in Lilongwe who were HIV positive was 73.3%, compared to 83.3% in Blantyre; but 90.9% of HIV positive patients in Lilongwe, compared to only 77.1% in Blantyre were on ART prior to presenting with TB. The median age of guardians was 32 years (IQR 26-40 years), and 30.4% were male. 56.4% of guardians had no formal education beyond primary school level.

Table 32 shows the characteristics of the study population according to randomisation arm. A lower proportion of patients randomised to receive community-based care were male (64.4 % v 74.8%); a higher proportion had pulmonary tuberculosis (95.2% v 83.2%); and the median CD4 count in the community arm was higher (255 v 161 cells/mm^3), however none of these differences were statistically significant. The characteristics of guardians enrolled into each group were similar.

Table 31. Characteristics of trial participants by study site

	Total study population n = 204 (%)	Blantyre n = 144 (%)	Lilongwe n = 60 (%)
Patient characteristics			
Patient age (median, IQR)	36.5 (30.0-44.0)	36.0 (31.0-43.5)	37.5 (28.5-44.0)
Patient sex (% male)	142 (69.6)	97 (67.4)	45 (75.0)
TB Class			
Pulmonary	182 (89.2)	125 (86.8)	57 (95.0)
Extra-pulmonary	22 (10.78)	19 (13.2)	3 (5.0)
TB Category			
Relapse	99 (48.5)	60 (42.7)	26 (43.3)
TAD	5 (2.5)	5 (3.5)	0 (0.0)
Fail	15 (7.4)	4 (2.8)	0 (0.0)
Other	85 (41.7)	75 (52.1)	34 (56.7)
HIV positive	164 (80.4)	120 (83.3)	44 (73.3)
Established on ART if HIV positive	131 (80.9)	91 (77.1)	40 (90.9)
No. of previous TB episodes			
1	174 (85.3)	121 (84.0)	53 (88.3)
2	28 (13.7)	21 (14.6)	7 (11.7)
>2	2 (1.0)	2 (1.4)	0 (0.0)
Baseline Karnofsky score (median, IQR)	90 (80-100)	90 (80-90)	90 (80-90)
History of alcohol excess	47 (23.7)	30 (20.8)	20 (33.3)
Guardian characteristics			
Guardian age (median, IQR)	32 (26-40)	30.0 (25.0-40.0)	33.0 (29.0-40.0)
Guardian sex (% male)	62 (30.4)	45 (31.3)	17 (28.3)
Guardian level of education			
None	4 (2.0)	3 (2.1)	1 (1.7)
Standard 1-4	33 (16.2)	12 (8.3)	21 (35.0)
Standard 5-8	52 (25.5)	38 (26.4)	14 (23.3)
Form 1-2	42 (20.6)	36 (25.0)	6 (10.0)
Form 3-4	45 (22.1)	36 (25.0)	9 (15.0)
University	28 (13.7)	19 (13.2)	9 (15.0)
Guardian relationship to patient			
Spouse	74 (36.3)	48 (33.3)	26 (43.3)
Sibling	56 (27.5)	41 (28.5)	15 (25.0)
Parent	16 (7.8)	6 (4.2)	10 (16.7)
Child	19 (9.3)	17 (11.8)	2 (3.3)
Aunt/Uncle	14 (6.9)	11 (7.6)	3 (5.0)
Niece/Nephew	9 (4.4)	8 (5.6)	1 (1.7)
Friend/neighbour	16 (7.8)	13 (9.0)	3 (5.0)

Table 32. Characteristics of trial participants according to study arm

	Total study population n = 204 (%)	Hospital-based Management n = 101 (%)	Community-based management n = 103 (%)
Patient characteristics			
Patient age (median, IQR)	36.5 (30.0-44.0)	37.0 (30.0-44.0)	36.0 (30.0-43.0)
Patient sex (% male)	142 (69.6)	77 (74.8)	65 (64.4)
TB Class			
Pulmonary	182 (89.2)	84 (83.2)	98 (95.2)
Extra-pulmonary	22 (10.78)	17 (16.8)	5 (4.8)
TB Category			
Relapse	99 (48.5)	44 (43.6)	55 (53.4)
TAD	5 (2.5)	2 (2.0)	3 (2.9)
Fail	15 (7.4)	5 (5.0)	10 (9.7)
Other	85 (41.7)	50 (49.5)	35 (34.0)
Sputum culture positive	80 (39.2)	38 (37.6)	42 (40.8)
HIV positive	164 (80.4)	87 (86.1)	77 (74.8)
Established on ART if HIV positive	131 (80.9)	70 (81.4)	61 (80.26)
CD4 count (cells/mm3; median, IQR)	177 (82-423)	161 (68-339)	225 (117-560)
No. of previous TB episodes			
1	174 (85.3)	88 (87.1)	86 (83.5)
2	28 (13.7)	12 (11.9)	16 (15.5)
>2	2 (1.0)	1 (1.0)	1 (1.0)
Baseline Karnofsky score (median, IQR)	90 (80-100)	90 (80-90)	90 (90-100)
History of alcohol excess	47 (23.7)	21 (21.1)	26 (26.3)
Guardian characteristics			
Guardian age (median, IQR)	32 (26-40)	33 (28-39)	30 (25-40)
Guardian sex (% male)	62 (30.4)	28 (27.7)	34 (33.0)
Guardian level of education			
None	4 (2.0)	4 (4.0)	0 (0.0)
Standard 1-4	33 (16.2)	20 (19.8)	13 (12.6)
Standard 5-8	52 (25.5)	26 (25.7)	26 (25.2)
Form 1-2	42 (20.6)	18 (17.8)	24 (23.3)
Form 3-4	45 (22.1)	20 (19.8)	25 (24.3)
University	28 (13.7)	13 (12.9)	15 (14.6)
Guardian relationship to patient			
Spouse	74 (36.3)	37 (36.6)	37 (35.9)
Sibling	56 (27.5)	28 (27.7)	28 (27.2)
Parent	16 (7.8)	9 (2.9)	7 (6.8)
Child	19 (9.3)	7 (6.9)	12 (11.7)
Aunt/Uncle	14 (6.9)	7 (6.9)	7 (6.8)
Niece/Nephew	9 (4.4)	3 (3.0)	6 (5.8)
Friend/neighbour	16 (7.8)	10 (9.9)	6 (5.8)

5.4.2 Successful completion of the intensive phase of treatment

At the end of the intensive phase of treatment, 97 (96%) of patients in the hospital arm and 96 (93.2%) of patients in the community arm were sill alive and on treatment (RD -0.03 (95% CI -0.09 – 0.03); p-value 0.538). Only an intention to treat analysis was performed, as all randomised patients received the form of treatment to which they are assigned. There were 7 deaths in the community arm, and 2 in the hospital arm (RR 3.43; 95% CI 0.73 – 16.13) (table 33). Deaths were reviewed at a meeting of the DSMB in September 2014, and it was concluded that none were either directly or indirectly related to the intervention. Of the 7 deaths which occurred in the community arm, 6 occurred after the patient had been readmitted to hospital (see table 34 for clinical details of all deaths). Two patients defaulted from hospital-based care, but none defaulted from community-based care.

Table 33. Treatment outcomes at 2 months

	Hospital-based management n = 101 (%)	Community-based management n = 103 (%)	p-value	RR (95% CI)
Alive and on TB treatment	97 (96.0)	96 (93.2)	0.54	0.97 (0.91-1.03)
Death	2 (2.0)	7 (6.8)	0.17	3.43 (0.73-16.13)
Default	2 (2.0)	0 (0.0)	0.24	NA

Table 34. Details of deaths during the intensive phase of treatment

Details of event	Location
Community-based treatment arm	
Stevens Johnsons syndrome 2 weeks after starting TB treatment, 1 week after starting ART	Hospital
End stage heart failure with dilated cardiomyopathy; on treatment for presumed TB pericarditis	Hospital
Acute febrile illness with jaundice; treated for presumed bacterial sepsis	Hospital
Disseminated Kaposi Sarcoma, pancytopenia, ascites, splenomegaly	Hospital
Headache, dysphasia, hemiparesis; treated for presumed cerebral toxoplasmosis	Hospital
Cryptococcal meningitis	Hospital
Sudden death	Community
Hospital-based treatment arm	
Died whilst receiving bowel prep for colonoscopy; presumed electrolyte imbalance	Hospital
Jaundice; presumed drug induced liver injury	Hospital

5.4.3 Secondary outcomes

End of TB treatment outcomes

Before the close of the study, the first 162 patients enrolled to the trial had completed 8 months of follow up and therefore had registered TB treatment outcomes. Clinical outcomes of these patients are shown in table 35. Of the patients who received community-based care during the intensive phase, 67/83 (80.7%) successfully completed the 8 month course of treatment, compared to 61/79 (77.2%) who received hospital-based care. The proportion of patients in the community arm who were cured was 49.4%, compared to 32.9% in the hospital arm (RR 1.50 (95% CI 1.02-2.20) p-value 0.04). There were no significant differences between the two groups in the numbers who failed, died or defaulted treatment.

Table 35. 8 month treatment outcomes

	Hospital-based management n = 79 (%)	Community-based management n = 83 (%)	p-value	RR (95% CI)
Successful treatment	61 (77.2)	67 (80.7)	0.70	1.05 (0.89-1.23)
Cure	26 (32.9)	41 (49.4)	0.04	1.50 (1.02-2.20)
Complete	35 (44.3)	26 (31.3)	0.12	0.71 (0.47-1.06)
Fail	1 (1.2)	1 (1.2)	1.00	0.95 (0.06-14.96)
Death	11 (13.9)	13 (15.7)	0.83	1.12 (0.54-2.36)
Default	4 (5.1)	2 (2.4)	0.43	0.48 (0.09-2.53)
Transfer out	2 (2.5)	0 (0.0)	0.24	NA

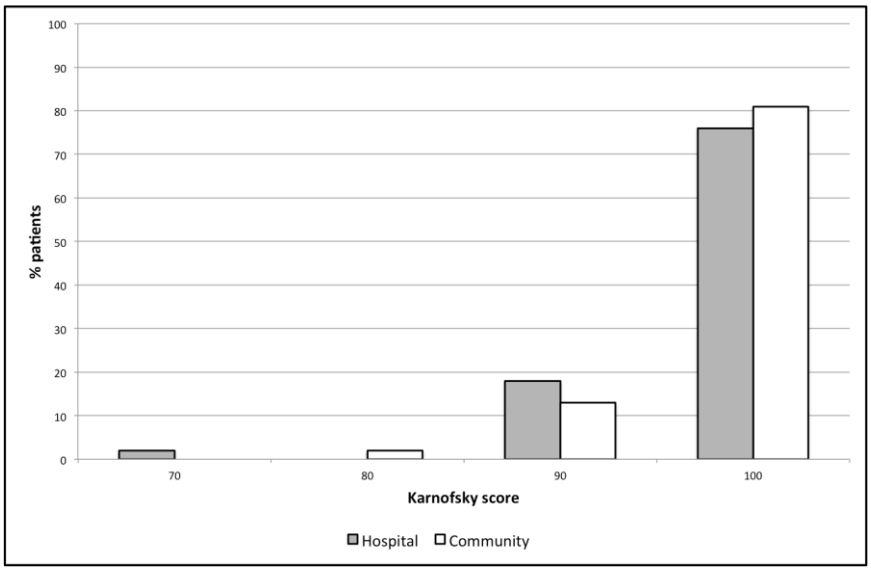
Two-month culture conversion

Of 80 patients who had sputum which was culture positive for *M. tuberculosis* at the start of treatment, repeat sputum culture was performed in a subgroup of 43 patients who were able to provide a sample after 2 months of treatment. In the group who received community-based care, 21/23 (91.3%) went from being sputum smear positive to sputum smear negative at 2 months, compared to 15/20 (75.0%) who culture converted in the hospital-based care group (RR 1.22 (95%CI 0.91-1.61); p-value 0.22).

Karnofsky score at the end of the intensive phase of treatment

The median Karnofsky score at the end of the intervention period was 100% in both groups. Of patients still alive at the end of the intensive phase of treatment, 84.4% in the community group and 79.2% in the hospital group had a Karnofsky score of 100% (figure 31). One patient in the hospital arm had a final Karnofsky score of 70, and one patient in the community arm had a final score of 80.

Figure 31. Final Karnofsky scores



Mental health status at the end of the intensive phase of treatment

All but one of the 21 patients who were identified as having common mental health disorder at baseline no longer scored above 7 on the SRQ after 2 months of treatment. The one patient who continued to screen positive for depression at the end of the intervention period had received hospital-based care.

5.4.4 Adverse events

There were 56 adverse events in 36 patients who received hospital-based care and 34 adverse events in 20 patients who received community-based care (table 36). All events were clinical events. One patient reported a missed dose of streptomycin and two patients missed a single dose by 'vial count', but there was no episode which met the pre-defined criteria for an adherence event. There were no needle stick injuries in either arm. Adverse events that resulted in death or default are reported as part of the primary outcome, hence are not discussed here. There were 8 serious adverse events in the hospital arm and 5 in the community arm. Both adverse events which resulted in potential disability were as a consequence of presumed ototoxicity and occurred in the hospital arm.

Table 36. Adverse events during the intensive phase of treatment

	Hospital-based management n = 101	Community-based management n = 103
Total Adverse Events	56	34
Serious Adverse Events	8	5
Life threatening illness	6	0
Hospitalisation	0	5
Significant disability	2	0
Needle stick injury	0	0

5.5 Discussion

This trial demonstrated that 93.2% of patients who received community-based care during the intensive phase of TB retreatment successfully completed 2 months of treatment, compared to 96.0% of those managed in hospital (Risk difference -0.03 (95% CI -0.09 - 0.03); p-value 0.538). There was no difference between the two study arms in terms of successful 8 month completion of TB treatment (80.7% in the community v 77.2% in the hospital); or the rate of 2 month culture conversion (91.3% in the community v 75.0% in the hospital), suggesting that overall outcomes at the end of treatment were comparable in the two groups.

5.5.1 Primary outcome

The risk difference between the two groups in the primary outcome of 'still alive and on treatment at 2 months' was only 3%. However, the confidence intervals around this estimate reached 9%, therefore non-inferiority cannot be concluded at a margin of 6% which was the pre-defined non-inferiority limit. These figures are open for interpretation and discussion. Firstly, a non-inferiority margin of 6% was rather conservative. The choice of non-inferiority margin is essentially subjective, with many other trials setting margins of 10% - 15% [413-416]. Had this trial chosen a higher margin, not only the point estimate for the risk difference, but also the 95% confidence intervals around that estimate may well have fallen within the limit set for non-inferiority.

Second, it is worth noting that the point estimate of 3% difference in risk is low, and that it is only the 95% confidence intervals which cross the chosen non-inferiority margin. The confidence intervals around this risk difference are wide primarily because the event rate in the study was low. This in itself is important to note - that the absolute rate of unsuccessful treatment in the community at 2 months was only 7%. This is a high rate of treatment 'success', with previous estimates of unsuccessful retreatment at 2 months in Malawi being as high as 13%.

Finally, in trying to assess "what works, for who, and in what circumstances?", it is important to consider "what *didn't work*, for who, and in what circumstances?". Whilst there were 7 deaths in the community arm of the study, compared to only 2 in the hospital arm (relative risk 3.43, 95% CI 0.73-16.13), the circumstances of these deaths need to be carefully examined. There could be a number of explanations for what may be a higher mortality rate in the community arm. The first explanation is chance: there is no statistical difference in the mortality rates between the two groups. Nevertheless, it is important not to ignore the fact that the absolute number of deaths in the community was nearly 3.5 times higher than in the hospital, and consider possible reasons for this. A higher death rate may have been as a direct consequence of guardians administering injections. However, none

of the deaths were related to unsafe administration of an intramuscular injection, such as overwhelming sepsis originating from an infection at the site of infection. Additionally, there is no evidence that adherence to treatment in the community arm was a problem, as both measures of adherence suggested very few missed doses of streptomycin; the rate of sputum culture conversion at 2 months was similar in both groups; and all of the deaths were due to conditions other than TB. A third possible reason for an increased death rate in the community may be that patients at home may suffer as a consequence of having less medical attention during the intensive phase of treatment. As has already been demonstrated in chapter 3, patients on TB retreatment are a complex group with multiple medical co-morbidities, and it may be that they benefit from regular clinical reviews whilst admitted to hospital, with community-based management having the effect of decreasing the level of care patients receive. Some evidence for this may be suggested by the higher number of adverse events in the hospital arm compared to the community arm, although this may have been expected as any prescription of medication by a physician was classified as an adverse event. However, it is well recognised that over-prescription of antibiotics and other drugs by clinicians in common [417, 418], and because patients were reviewed twice a week on the ward, it is unsurprising that they were prescribed medications more frequently. An alternative explanation for the higher number of prescriptions in the hospital group is the transmission of nosocomial infections, and further limitation of this study was its inability to accurately capture data about confirmed hospital acquired infections.

An indirect effect of community-based care also seems unlikely though for other reasons. Of the seven deaths in people randomised to the community arm, six happened only following readmission to hospital. In 5 out of 6 of these patients, the death took place after they had been receiving appropriate treatment as an in-patient for at least 7 days. For example, it is hard to see how a patient with cryptococcal meningitis who complained only of mild headache and was well enough to walk into the ward for readmission but deteriorated despite appropriate treatment with fluconazole, amphotericin and therapeutic lumbar punctures, would have had any different outcome had she been managed in the hospital. Similarly, a

patient treated for 'TB pericarditis' who was later found to have end-stage dilated cardiomyopathy and treated with intensive diuresis as an in-patient for 2 weeks prior to his death, was likely to have had a poor outcome in any setting.

5.5.2 Secondary outcomes

Whilst analysis of the primary outcome is open to interpretation, the data on secondary outcomes in this study are very encouraging. Crucially, end-of-treatment programmatic outcomes at 8 months were the same in both groups. Ultimately, it is the successful completion of the full course of TB treatment, rather than an intermediate outcome after 2 months, which is important from both individual and programmatic perspectives. In this case, a primary outcome at 2 months was chosen only because the time constraints of the PhD fellowship did not allow for an additional 6 months of patient follow up for all patients. Of the total cohort, 8-month treatment outcome was known in 79%, and the proportion who successfully completed treatment was 80.7% in the community arm, compared to 77.2% in the hospital arm. There were no significant differences in treatment outcome group between patients in the two study arms, apart from a higher cure rate in the community arm, which is difficult to explain. Overall Karnofsky scores and SRQ scores were high in both groups throughout the study, precluding any meaningful assessment of the differences in changes in performance status and mental health between the groups.

5.5.3 Study limitations

The major limitation of this study was its failure to demonstrate statistical non-inferiority and the decision of the TSC to stop the trial early due to futility. The reasons for this are two-fold. Although every effort was made to predict the expected event rate by conducting a review of the QECH TB register prior to starting the study, the eventual event rate was much lower than had been predicted. This can be explained by the fact that the trial recruited a cohort of patients who were less sick than the general group registering for retreatment, as by definition they

had to be well enough to be discharged. As evidenced by the very low rate of default before completion of treatment (5.1% in the hospital group and 2.4% in the community group), this trial also recruited a self-selected group of participants who were motivated to be involved in their own health care and take an active role in their treatment. Additionally, it is common for clinical outcomes in a trial setting to be better than those in routine practice, due to increased input from the study team. Despite intentions to maintain routine conditions, this may also have played a role in improving outcomes across the board in patients recruited to the TB-RROC trial.

A possible source of bias in this study is that despite randomisation there were some slight differences in baseline characteristics between the two groups. The HIV prevalence in the community arm was 74.8% compared to 86.1% in the hospital arm, with a median CD4 count of 225 cells/mm^3 compared to 161 cells/mm^3; and the proportion of patients with pulmonary TB was 95.2% compared to 83.2% in the hospital arm. These differences were small and none were significantly different on statistical testing, never the less it is important to recognise them.

According to realist approaches to evaluation, it is important not simply to present an overall statistical analysis of an intervention, but rather to examine some of the mechanisms underlying outcomes in order to understand how and why the intervention has impact. In this instance, a realist evaluation may have examined how community-based management worked differently for different people, and perhaps performed subgroup analyses according to gender, HIV status or study site. A further limitation of the study from a realist perspective is that it was not sufficiently powered to perform subgroup analyses which would have made this possible, and instead these issues are addressed in the economic and qualitative evaluations (Chapters 6 and 7).

When trying to decide who an intervention does *not* work for, an important group to consider is those who were not recruited. This study had a higher rate of non-uptake than predicted in the development stage or suggested by the pilot study,

with only 44.7% of those initially screened for eligibility eventually randomised. There were no differences in age or gender between those who were and those who were not randomised. As the low recruitment rate was not predicted, data were not collected about any additional characteristics which may have shed light on the reasons people did not participate. The commonest reasons for non-enrolment were that either the patient or the guardian declined to participate. It has long been recognised that recruitment rates to trials are frequently lower than predicted. In the 1970s, Louis Lasagna, an American pharmacologist, recognised the phenomenon which became known as 'Lasagna's Law.' The law states that "the incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed" [419]. It is not uncommon for clinical trials to fail to reach recruitment target, with one review of studies published in the Lancet and British Medical Journal demonstrating that nearly 60% of trials either failed to meet the target recruitment or required an extended period of recruitment [420]. A number of potential barriers to recruitment to clinical trials have been described and include a lack of trust in medical research, poor understanding of the medical diagnosis and/or intervention, and practical issues such as time commitment or transportation [421, 422]. Strategies which are thought to increase recruitment to clinical trials include unblinded studies, monetary incentives and culturally appropriate study designs [423], as well as telephone reminders and opt-out strategies [424]. The current study was unblinded and designed specifically to be employed in a Malawian setting. Monetary incentives were considered, however it was believed that as this was not something which would be offered under routine conditions, it was not appropriate to offer incentives during the study. As many of the recognised barriers to recruitment are specific to the research process, it is always interesting to consider what might happen if the intervention were introduced in a non-research setting, which may be an argument for additional evaluation under programmatic conditions in this instance.

The low recruitment rate to the TB-RROC trial may impact on the generalisability of the results, as they only apply to fewer than half of the patients who started TB

retreatment during the period of recruitment. In addition to patients and guardians declining to participate, a significant proportion of patients were not recruited because they were never clinically stable enough to be discharged. As well as the 21 patients who were medically unfit and the 10 patients who died following enrolment, a number of those who were recorded as having declined to participate did so because they were not well enough to do so. However, it was never intended for the intervention to be applicable to all patients who are prescribed TB retreatment, and even under routine conditions only those well enough to go home would be considered for community-based management. In other respects, the trial was designed to be as generalisable as possible, and the pragmatic approach to its design has already been discussed in some detail in chapter 2.

5.6 Conclusion

Although there are many published evaluations of community-based management for patients receiving standard 6 month short course chemotherapy and patients being treated for MDR-TB, this is the first evaluation specifically concerned with community-based management of patients on retreatment regimen. It is also the first study to investigate training guardians (lay people) rather than health professionals to deliver parenteral antibiotics in a low resource setting. The results of this study are in keeping with the literature in showing that adherence to treatment in the community is good; guardians are able to deliver injections safely with out causing infection or sciatic nerve injury; and outcomes at completion of TB treatment are comparable to hospital-based care.

Ultimately in non-inferiority studies, it is the job of decision makers to assess whether they are willing to accept the possible risks involved in the new intervention. In the current situation, their question would be: “is a 3% (or, worst case, 9%) increased risk of death or default during the first 2 months of TB retreatment a risk worth taking, given similar outcomes at the end of TB treatment, and the potential advantages of community based care?” The main theory driving the evaluation of this intervention is that there are indeed benefits for both

patients and health systems of community-based care during the intensive phase of TB retreatment, and the next two chapters of this thesis investigate those potential financial and social benefits. The final chapter then combines the data from all modalities of evaluation to make an overall assessment of the intervention, provide recommendations and make suggestions for further work.

6 The TB-RROC Trial Economic Evaluation

6.1 Introduction

Having examined the clinical outcomes of hospital and community-based management during the intensive phase of TB retreatment, this chapter moves on to look at the economic consequences of the TB-RROC intervention. A full economic analysis from a societal perspective was performed in order to provide data for use in decision-making, as well as to evaluate the financial outcomes of community-based management on study participants and their households.

6.2 Aims and objectives

The broad aim of this study was to evaluate the health economic consequences of hospital and community based management of patients during the intensive phase of TB retreatment in Malawi.

The primary objective was:

To determine the cost effectiveness of a community based model of care using guardians to deliver streptomycin to patients during the intensive phase (first 2 months) of TB retreatment in Blantyre, by performing a trial based economic evaluation of community versus hospital based care.

Secondary objectives were:

1. To assess health utility at the end of the intensive phase of TB retreatment, and compare health utility in patients who received community-based management to those who received hospital-based management.
2. To estimate costs and health care resource use during the continuation phase of TB retreatment; and to compare costs and resource use between

participants who received hospital-based and those who received community-based care during the intensive phase of TB retreatment.

3. To document broader economic consequences for households of people receiving retreatment regimen for TB in Blantyre and Lilongwe, including catastrophic costs.

6.3 Methods

6.3.1 Study design

The main study was a trial-based economic evaluation, nested within the TB-RROC trial. It took a societal perspective, and total costs were broken down into health system and user costs. Results are presented using incremental cost effectiveness ratios and expressed in terms of incremental costs per patient successfully completing 2 months of treatment [425]. Additional data on 8 month costs, financial effects on households, and usage of health facilities were also collected from trial participants, and examined in separate analyses. The household economic consequences of an episode of TB retreatment were evaluated according to the socioeconomic position of the study participants.

6.3.2 Estimating user costs

User costs of community-based care were estimated by interviewing study participants at the end of the 2 month intervention period. Data were collected using a standard proforma. This had been developed based on a tool for determining user costs during TB care which has previously been used extensively in Malawi [426]. User costs included only costs incurred after the start of TB treatment - it was assumed that costs associated with the process of being diagnosed with TB were the same in both arms of the trial, as the intervention began only after a diagnosis had been made. Costs were broken down into direct medical and non-medical costs. Direct non-medical costs included costs of food, transport and linen. Additionally, indirect costs (productivity losses) for the patient

and guardian were calculated by multiplying the number of days of admission (for patients) or days of missed work (for guardians) by reported daily income. As part of the questionnaire, study participants were asked what their average weekly income was prior to the onset of illness, from which an estimate of average daily income was derived. For participants in the community arm, direct and indirect costs from additional visits to health care facilities after discharge were estimated for both the patient and guardian.

6.3.3 Estimating provider costs

6.3.3.1 Estimating provider costs of the intervention

Costs were calculated using a 'bottom up' ingredients approach. All resource use was prospectively documented during a defined period of the trial. Values were determined for each unit of resource, and then total cost was calculated by multiplying the total resource use by the cost per unit.

The health system costs of community based care were broadly divided into (1) costs of training staff; (2) costs of training guardians to deliver intramuscular streptomycin; (3) costs of routine follow up in the community; (4) costs of unscheduled attendances (adverse events); and (5) costs of TB drugs (figure 32). For each of these units, resource use was estimated prospectively, and the value of each resource item calculated using the tools outlined in tables 37-40. The cost of training staff was added to staff salaries for analysis. Data were used to calculate the total costs of care for all patients during the period of evaluation, from which an estimate was derived for the cost per patient successfully treated. Overhead costs were estimated as a proportion of the total costs of running a medical ward, based on the staff time spent on training and follow up of patients managed in the community. Staff salaries were estimated using data from QECH for staff at the equivalent level (e.g. fieldworker costs were estimated using the salary of a TB officer/HSA at QECH). Drug costs were calculated based on the 2013 MSH International Drug Price Indicator Guide [427].

Figure 32. Components of health system costs of community based care

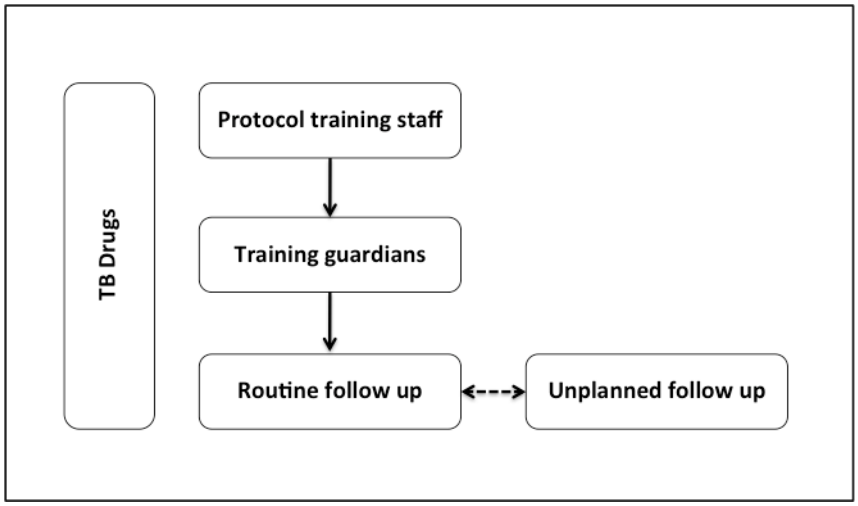


Table 37. Resource use and costs of training study staff

Staff protocol training		
	Method to estimate resource use	**Method to estimate resource cost**
Staff time (doctor delivers training)	Training timetable: hours spent training; plus preparation time	Doctor (lecturer) salary at Malawi CoM
Staff time (study staff get trained)	Training timetable: hours spent training	QECH staff salary scale
Stationary	Number of training folders produced	Costs of items at MLW stores
Refreshments	Training timetable: one lunch break	Costs of lunch allowance at MLW

Table 38. Resource use and costs of training guardians to do injections

Training guardians		
	Method to estimate resource use	**Method to estimate resource cost**
Consumables	Records kept prospectively by study nurse during training of guardians	Cost of items purchased through MLW or WTTC as applicable
Nurse time	Records kept prospectively by study nurse during training of guardians	QECH staff salary scale
Hospital admission	Data recorded routinely as part of TB-RROC trial	Cost of admission day for retreatment (See section 6.3.3.2)

Table 39. Resource use and costs of routine community follow up

Routine follow up		
	Method to estimate resource use	**Method to estimate resource cost**
Consumables	Records kept by fieldworker whilst doing community visits	Cost of items purchased through MLW or WTTC as applicable
Fieldworker time	Records kept by fieldworker whilst doing community visits	QECH staff salary scale
Transport	Records of minibus usage kept by fieldworker on community visits	Records of minibus cost kept by fieldworker on community visits

Table 40. Resource use and costs of adverse events in the community

Adverse events		
	Method to estimate resource use	**Method to estimate resource cost**
Staff time	Records kept prospectively by staff (fieldworker, nurse, clinician)	QECH staff salary scale
Admission time	Records kept of number of days in hospital following readmission	Cost of admission day for retreatment (See section 6.3.3.2)
Transport	Records of minibus usage kept by fieldworker on community visits	Records of minibus cost kept by fieldworker on community visits
Tests	Records kept prospectively by study nurse/clinician of all tests performed	Costs of tests at QECH (See section 6.3.3.2)
Drugs	Records kept prospectively by study nurse/clinician of all drugs, dosages & duration prescribed	Most up to date version of International Drug Price Indicator Guide (supplier median price)

6.3.3.2 Estimating provider costs of standard of care

The costs of providing hospital-based care during the intensive phase of TB retreatment were only estimated at the Blantyre site (QECH). A full hospital costing study of patients admitted to QECH (The Cost HTC Study) was being undertaken by a collaborator at MLW (Dr H Mahesweran) at the same time as the TB-RROC trial was being conducted. The Cost HTC Study recruited a sample of 1 in 5 admissions to the adult medical wards at QECH in order to estimate the costs of admission for

specific medical conditions, including tuberculosis. The Cost HTC study population was enriched for patients receiving TB retreatment by additionally including all patients randomised in the TB-RROC trial to receive hospital-based care during a one year period. The methods employed to estimate the costs of a hospital admission were as outlined by Dr Mahesweran below.

Medical data extraction

A medical doctor reviewed the notes of all participants and extracted data about the medical care which the patient received using a standard proforma which had been developed by discussion with doctors at QECH and piloted before use. The duration and outcome of admission and were noted. Data were extracted about which investigations and procedures were performed and how often they were performed. For prescriptions, drug name, dosage, frequency, route of administration and duration were recorded.

Cost analysis

The costs for all medical resources used were determined based on the UNAIDS costing guidelines [428]. A bottom-up approach was used to estimate the cost of medical resource outputs at QECH (e.g. a day of admission, a full blood count). The first step in the process was to generate a list of medical resource outputs. Secondly, interviews were conducted with medical and administrative personnel to identify the individual resource inputs (e.g. needles, syringes) required to produce each medical resource output. Thirdly, financial data from the hospital administration systems, in combination with national and international resources, were used to value the individual resource inputs. These data were then used to calculate the cost of each medical resource output. Finally, the estimated resource output costs were used to generate the total health provider cost for each patient.

A top-down method was also used to allocate the additional costs of support services for each medical resource output. Interviews were undertaken with central

support services to estimate the total cost of support services for the hospital, which included the costs of central administration, cleaning, portering, security, laundry and catering services. The total costs of these support services were then divided amongst the departments involved in providing care to adult medical patients i.e. medical wards, laboratory, radiology and pharmacy. This was done by dividing the number of staff working in each department by the total number of staff working in the hospital and allocating costs proportionately.

In order to estimate the cost of a day of admission to an adult medical ward, interviews were conducted with the nurse in charge of each ward. Data were obtained about the number of staff on the ward and the hours they worked; as well as consumable use and equipment on the ward. The total costs per year were estimated, and the costs of central support services were added to this cost (see above) in order to estimate the total annual cost of running the ward. During the period of the Cost HTC Study, the number of patients on each ward was recorded daily. By dividing the total annual cost of running the ward by the total number of patient days, the average ward stay cost for one day of admission was estimated.

A similar process was employed to estimate a prescription cost for drugs dispensed from the hospital pharmacy. By interviewing staff in the pharmacy department, the total cost of resource inputs was estimated, to which the costs of central support services was added. The pharmacy has a record of all drugs it supplies, which was then used to calculate the average cost per drug dose dispensed.

Direct and indirect costs of investigations performed at the laboratory and radiology departments were estimated. Direct costs included the costs of consumables, equipment and personnel time involved in the procedure; and were estimated based on interviews with the staff involved. Indirect costs were estimated based on the total annual cost of running the department plus central support services. The annual cost of running the department was once again based on interviews with staff, which established the amount of time staff spent at work but not directly involved in performing specific procedures, as well as the total consumable and

equipment use. The indirect costs of each procedure were estimated by dividing the total number of procedures performed in a year by the total indirect annual costs. Adding the direct and indirect costs of each procedure produced an estimate of the average cost for each procedure. For procedures performed by clinicians on the wards, only the direct costs were estimated. For investigations performed outside QECH, the cost charged to QECH was used (e.g. CT scans, MRI scans).

For all the costing, staff salaries were obtained from the QECH human resources department and included employer contributions and fringe benefits. The costs of consumables and equipment were obtained from the Malawi Ministry of Health price catalogue. For costs that were not available in the catalogue, international or reference prices were used. For this, first local suppliers were contacted to obtain costs, and if not available, international suppliers and manufacturers were contacted. Equipment costs were annuitized over their useful life with an annual discount rate of 3%. For large laboratory and imaging equipment, useful life was assumed to be 5 years. This assumption was based on discussions with laboratory and radiology staff on time before equipment would be replaced. For all other equipment's, including general office equipment, useful life was assumed to be 3 years.

6.3.4 Estimating outcomes of the intensive phase of TB retreatment

6.3.4.1 Effectiveness outcome

The outcome of interest for the primary analysis was successful completion of the intensive phase of TB retreatment. Patients who died or defaulted during the 2 month study period were classified as having an unsuccessful outcome; all those who were still alive and taking treatment after 2 months were deemed to have successfully completed the intensive phase of retreatment. The cost per person successfully completing 2 months of TB retreatment was estimated. These clinical outcome data were routinely collected as part of the TB-RROC trial.

6.3.4.2 Health-related quality of life outcome

A secondary analysis evaluated the health-related quality of life in each arm of the study. Utility scores for study participants were generated using a Chichewa validated version of the EQ-5D approved by the EuroQol group. The EQ-5D consists of two components: a 5-point descriptive scale in which participants are asked about their mobility, self-care, daily activities, pain and anxiety; and a visual analogue scale (VAS) in which patients are asked to score their health status by marking on a scale between 0 and 100 [429]. Descriptive scores provide individual health states for each participant, which are then converted to utility scores using conversion tariff sets which have been validated using national surveys of the general population. Estimation of the index values in this study was performed using the Zimbabwe-specific value set, as there is currently no validated tariff for Malawi and Zimbabwe is the country with a validated scale whose characteristics most closely resemble those of Malawi. Individual components of the descriptive scale are also presented individually. They were first converted into binary outcomes: “some problems” or “no problems” because the frequency of any problems with each modality was low.

6.3.5 Estimating costs and outcomes at the end of TB retreatment

Successful 8 month treatment outcome was assessed according to operational definitions as set out by the WHO. The standard definition of successful TB treatment comprises ‘cure’ or ‘treatment complete’. These outcomes were determined by reference to the TB register. Where data in the TB register were incomplete, patients were actively followed up by the study team using locator information provided at recruitment.

Data were collected from participants when they completed treatment at 8 months by administering a standard questionnaire. The questionnaire was similar to the one performed at 2 months, and was used to collect data from study participants about costs incurred during the six month period in which they were on

continuation phase TB treatment. They were asked about additional days of hospital admission, as well as outpatient attendance at the TB office, ARV clinic, Health Centre and Hospital outpatient or emergency department. Direct medical and non-medical user costs, as well as income lost due to additional days in hospital were calculated using the same methods applied to evaluating user costs during the intervention period. Participants were asked about overall costs of an average visit to each outpatient department, and these were multiplied by the total number of visits.

The evaluation of provider costs during the continuation phase of treatment was not within the scope of this study. The number of days of readmission as well as the number of attendances at ART clinic, TB office, out-patient department and A&E were documented. If the *number* of additional contacts with health services was similar in both groups, it was assumed that provider costs were likely to be similar in the two groups.

6.3.6 Evaluating Catastrophic household costs

The household economic situation of study participants was assessed at 2 months. Data were collected from participants at both sites. Total costs were defined as both direct medical and non-medical costs as well as indirect costs, and were calculated as a proportion of total annual household income. Total household income was estimated by multiplying the monthly household income by 12.

The term ‘catastrophic cost’ is used to describe healthcare costs which force households to reduce expenditure to a level which is below a basic minimum. There is not a currently a universal definition of what constitutes a ‘catastrophic cost’ and options have incorporated financial shock mechanisms (selling or borrowing) – sometimes referred to as ‘dissaving’ [430]; thresholds of total household income; and thresholds of ‘capacity to pay’ (the effective income for non-food expenditure). In this study, the primary definition of catastrophic cost was total health associated costs ≥10% of annual household income as this is a quantifiable measure which is

commonly used [34, 431, 432]. In a limited sensitivity analysis, data are also presented for the proportion of participants experiencing health expenditure of ≥20% or more of their total household income, given that this has been shown to correlate with poor tuberculosis treatment outcomes and may therefore be a more appropriate measure for patients with TB [275].

Wealth quartiles were generated using Principal Component Analysis [433, 434]., with the fourth quartile being the poorest and the first being relatively the richest. Components included in the analysis were based broadly on those in a proxy means test for poverty derived from the Malawi 1998 DHS [435], and are shown in table 41. Wealth scores were generated separately for participants living in urban and rural areas. Patients were asked to describe if they lived in a rural area, using the term *'Kumudzi'* in Chichewa, which roughly translates to 'home village', and broadly connotes rural dwelling. The proportion experiencing catastrophic costs are presented for each wealth quartile.

Dissaving activities are described in detail. The proportion of participants who borrowed money is reported, as well as descriptions of the loans including from whom people borrowed, and whether they were required to pay interest. Additionally, details of any property that was sold whilst the patient was on TB treatment are reported. Dissaving mechanisms are examined according to study arm and associations with wealth are described. Finally, the associations between dissaving and experiencing catastrophic costs are explored by calculating risk ratios for catastrophic costs in those who borrowed money or sold property in order to cover healthcare associated costs.

Table 41. Variables included in wealth score for principle component analysis

Rural	Urban
HH cooks over collected firewood	HH owns a fridge
Household size	Household size
Education level of household head	Age of head of household
No. of salaried HH members	Education level of household head
HH owns a bicycle	No. of salaried HH members
HH owns a car or motor cycle	HH owns a car or motor cycle
HH owns a fridge	HH gets lighting from electricity or gas
Purchased sugar in the last 2 weeks	HH owns a bed
Total acreage cultivated	
HH grows tobacco	
HH owns a bed	
No. cattle owned	

** HH = Household*

6.3.7 Currency, price and date conversion

Costs were recorded as the expenses incurred by the trial in Malawi Kwacha, Pounds Sterling or US dollars, and the year the cost was incurred was noted. The costs were adjusted to the year of reporting using the Gross Domestic Product deflator index, provided by the World Bank. All costs were converted into 2014 US Dollars using the market exchange rate.

6.3.8 Statistical analysis

For all cost data, means with corresponding 95% confidence intervals are presented. As cost data and EQ-5D scores were skewed, non-parametric bootstrap methods were used to derive 95% confidence intervals for the mean differences between these values in the two study arms.

Factors associated with incurring catastrophic costs were evaluated in univariate analysis and then multivariate analysis using a logistic regression model and controlling for pre-defined variables age, gender, HIV status, residence and wealth. The associations between catastrophic cost and clinical outcome were assessed

using a logistic regression model and adjusted for wealth. When it became clear that HIV was independently associated with incurring catastrophic costs, the model was adapted to also control for HIV. Risk ratios and 95% confidence intervals were calculated for the risk of incurring catastrophic costs according to study arm.

6.4 Results

6.4.1 Cost effectiveness of community-based management

6.4.1.1 User costs

Data about user costs during in the intervention were available for 188 out of the 204 (92.2%) participants enrolled into the trial. There were 11 patients no longer in care two months after starting treatment (9 patients died and 2 defaulted treatment); and a further five who were unable or unwilling to provide information.

Costs incurred by patients and guardians during the first two months of TB retreatment are presented in table 42, and the distribution of total costs in figure 33. The mean cost to participants who received standard of care was US$ 271.6, compared to a mean cost of US$ 101.8 for those who received community-based care. The mean difference between hospital and community-based care was US$ 169.8 (95% CI US$ 128.9 - US$ 210.7). The biggest out-of-pocket expense was food. The mean expenditure on food was 2.7 times higher for patients (US$ 69.8 v US$ 26.7) and 1.4 times higher for guardians (US$ 17.7 v US$ 13.6) in the group managed in hospital. Similarly, mean transport costs were higher for both patients and guardians who received hospital-based care: US$ 3.6 v US$ 1.6; and US$ 10.0 v US$ 6.4 respectively.

On average, lost earnings experienced by patients in the hospital arm were 3.4 times higher than those experienced by patients in the community arm. Patients in the community arm spent a mean of 17 days in hospital, whereas patients in the hospital arm spent a mean of 60 days in hospital. Guardians caring for patients in hospital lost a mean of 26.4 days earnings, whereas those in the community lost a

mean of only 12.2 days earnings during the time that their patient was admitted. There were 21 additional contacts with health care facilities after discharge in the group receiving community-based care, each visit taking an average of 5.5 hours for the patient, including travel and waiting times. Guardians accompanied patients on 13 out of the 21 visits to health facilities post-discharge, and lost on average 8.6 hours per visit. Overall, lost earnings experienced by guardians were much lower than those experienced by patients, but were again higher in those who received hospital based care. Of note, 66.7% (124/186) of guardians had no regular income.

Figure 33. Distribution of total user costs by study arm

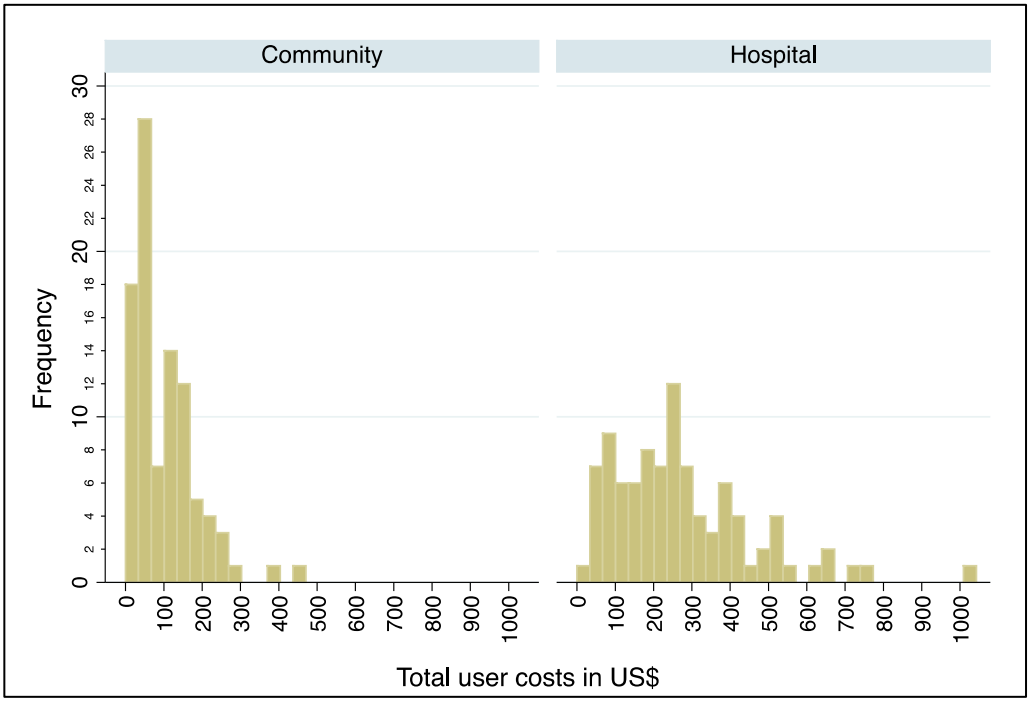


Table 42. Total user costs of hospital-based and community-based management during the intensive phase of TB retreatment

	Mean cost US Dollars (95% CI)		
	Hospital-based management	**Community-based management**	**Mean difference ***
Patient costs			
During admission			
Direct medical	0.7 (0.2-1.2)	0.4 (0.0-0.7)	0.3 (-0.2-1.0)
Direct non-medical			
Food	69.8 (58.4-81.2)	26.7 (21.5-31.8)	43.1 (30.5-55.7)
Transport	3.6 (1.6-5.7)	1.6 (0.5-2.6)	2.1 (-0.1-4.3)
Linen	0.7 (0.1-1.3)	1.1 (-0.1-2.3)	-0.5 (-1.8-0.9)
Other out-of-pocket	11.9 (7.1-16.7)	4.7 (3.2-6.2)	7.2 (2.1-12.4)
Indirect	133.5 (111.6-155.4)	37.0 (28.7-45.3)	96.5 (73.2-119.7)
Health facility post discharge			
Direct medical & non-medical	-	1.1 (0.3-2.0)	-1.1 (-2.0--0.3)
Indirect	-	0.3 (0.1-0.5)	-0.8 (-1.8-0.1)
TOTAL PATIENT COSTS	220.2 (189.8-250.8)	72.9 (60.5-85.3)	147.4 (114.1-180.6)
Guardian costs			
During admission			
Direct non-medical			
Food	17.7 (11.1-24.2)	13.6 (9.2-17.9)	4.1 (-3.5-11.7)
Transport	10.0 (5.6-14.3)	6.4 (4.1-8.8)	3.5 (-1.2-8.2)
Linen	0.1 (-0.1-0.2)	0.1 (0.0-0.3)	0.0 (-0.3-0.2)
Other out-of-pocket	2.9 (1.1-4.7)	1.6 (0.7-2.5)	1.3 (-0.7-3.4)
Indirect	20.6 (8.4-32.9)	5.2 (2.8-7.7)	15.4 (3.1-27.7)
Health facility post discharge			
Direct non-medical	-	1.0 (-0.6-2.7)	-1.0 (-2.7-0.6)
Indirect	-	0.8 (-0.1-1.8)	-0.8 (-1.8-0.1)
TOTAL GUARDIAN COSTS	51.3 (31.8-70-8)	28.6 (21.5-36.2)	22.4 (2.2-42.7)
TOTAL USER COSTS	**271.6 (234.4-308.7)**	**101.8 (85.1-118.4)**	**169.8 (128.9-210.7)**

* Bootstrapped estimates of Mean differences and 95%CI

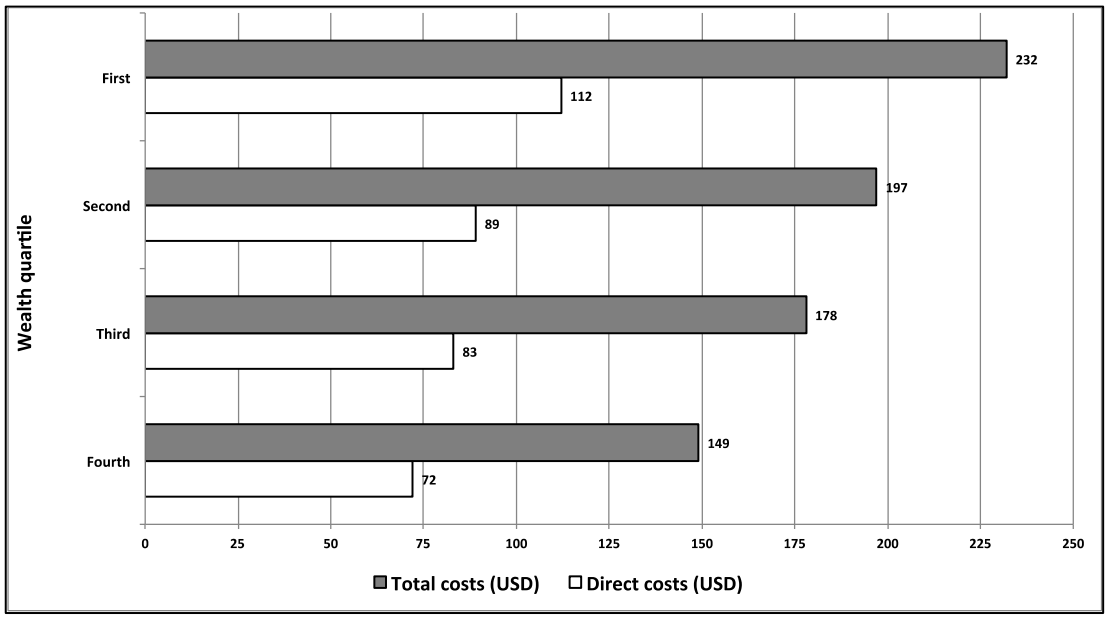
Costs were examined by wealth quartile. The characteristics of the participants in each wealth quartile are shown in table 43. The proportion of households owning a fridge and owning a television increased with increasing wealth quartile (chi^2 test for trend p values <0.001); and the proportion with earth floors in their houses decreased with increasing wealth quartile (chi^2 test for trend p-value <0.001). The mean monthly income increased as wealth quartile increased, but the mean monthly income in the 'richest' households was still only US$ 134.3 (95% CI US$ 93.2 – US$175.4).

Table 43. Characteristics of study population by wealth quartile

Wealth quartile	Household owns a fridge	Household owns a TV	Earth floor in house	Mean monthly household income (US$)
Fourth n=50 (%)	2 (4.0)	4 (8.0)	25 (50.0)	69.1
Third n=50 (%)	6 (12.0)	14 (28.0)	9 (18.4)	96.7
Second n=50 (%)	14 (28.0)	31 (62.0)	3 (6.1)	111.1
First n=49 (%)	41 (83.7)	41 (83.7)	1 (2.0)	134.3

In the study cohort as a whole, direct costs accounted for approximately half the total costs incurred during the first 2 months of TB retreatment, with lost earnings accounting for the other half (figure 34). The mean total costs for patients and guardians increased with increasing wealth quartile (chi^2 test for trend p-value 0.04), with the first quartile spending a mean of US$ 232 and the poorest quartile spending a mean US$ 149 (figure 34). Similarly, the average direct costs to users, increased with increasing wealth quartile – the mean loss in the first quartile was US$ 112 compared to a mean loss in the poorest quartile of US$ 72 (chi^2 test for trend p-value 0.07).

Figure 34. Mean user costs according to wealth quartile



6.4.1.2 Provider costs

Costs of community-based care

Data on the provider costs for the intervention were available for 32 patients. The costs of community-based care are shown in table 44. The mean cost of community-based care was US$ 498.0 (95% CI 425.6-570.4) per patient. The majority of the cost of the intervention was accounted for by the costs of the patient being admitted to the ward whilst the guardian was being trained to administer injections. The mean number of days that patients remained on the ward prior to randomisation and discharge was 17 days (range 4 days – 53 days). Costs of TB drugs (US$ 85.4) and ART (US$ 20.5) combined were the second largest expense. In total, there were 12 adverse events, costing a mean of US$ 34 each. There were 2 readmissions, one lasting 15 days (cost US$ 217) and the other lasting 34 days (cost US$ 492).

Table 44. Provider costs of community based care during the first 2 months of TB retreatment

	Mean costs (95% CI) 2014 US dollars n=32
Training guardians	
Days of admission	301.0 (233.0-369.1)
Nurse time	7.5 (5.8-9.3)
Gloves	1.2 (0.8-1.5)
Syringes	0.4 (0.3-0.5)
Needles	0.8 (0.7-1.0)
Water for injection	0.7 (0.6-0.9)
Alcohol swabs	0.2 (0.2-0.3)
Training materials	1.2
Overhead costs	1.3 (1.0-1.6)
TOTAL TRAINING COSTS	314.3 (245-383.0)
Routine follow up	
HSA time	9.7 (7.8-11.6)
HSA transport	7.4 (5.4-9.5)
Gloves	5.6 (5.0-6.2)
Syringes	2.7 (2.4-3.0)
Needles	3.1 (2.8-3.4)
Water for injection	4.6 (4.2-5.1)
Alcohol swabs	1.2 (1.0-1.3)
Sharps boxes	4.6 (4.3-5.0)
Overhead costs	4.9 (3.9-5.9)
TOTAL FOLLOW UP COSTS	43.9 (38.0-49.7)
Adverse events	
HSA time	0.1 (0.0-0.2)
Nurse time	0.01 (0.0-0.1)
Junior clinician time	0.1 (-0.1-0.4)
Senior doctor time	0.5 (0.1-1.0)
Drugs	3.7 (-2.2-10.0)
Investigations & procedures	6.8 (-1.5-15.1)
Ward stay for readmission	22.2 (0.0-56.1)
Airtime	0.3 (0.0-0.6)
Overhead costs	0.1 (0.0-0.2)
TOTAL ADVERSE EVENT COSTS	34.0 (0.0-75.7)
TB drugs	85.4 (80.9-89.8)
ART	20.5 (19.4-21.6)
TOTAL PROVIDER COSTS	**498.0 (425.6-570.4)**

A summary of the costs of hospital-based care are shown in table 45. The mean cost to the health service of providing hospital based care was US$ 1100.3 (95%CI US$ 1040.8 –US$ 1159.8) per patient. The bulk of the expense was accounted for by general costs of running the ward, which accounted for 81% of the total cost of hospital-based care during the intensive phase of retreatment.

Table 45. Provider costs for hospital-based care during the first 2 months of TB retreatment

	Mean costs (95% CI) 2014 US dollars n=33
Investigations & procedures	109.2 (68.5-149.9)
Drugs	114.0 (110.1-117-9)
Ward stay	895.6 (859.1-932.1)
TOTAL PROVIDER COSTS	**1100.3 (1040.8-1159.8)**

6.4.1.3 Cost effectiveness of the intervention

It was possible to estimate total costs of care only for the 65 patients in whom data about health provider costs were available. Of the 33 patients who received hospital-based care, 31 successfully completed 2 months of treatment (1 default; 1 death); and of 32 who received community-based care, 30 successfully completed 2 months of treatment (2 deaths). User costs were not available for the three patients who died and one who defaulted prior to completion of the intensive phase of retreatment. For these patients, the mean user cost of either hospital or community based care respectively was used. In a limited sensitivity analysis, these costs were replaced with the minimum and maximum user costs for each group.

Table 46 shows the total costs of community-based and hospital-based care during the intensive phase of TB retreatment. The total cost of care for 33 patients managed in the hospital was US$ 47,936.6, which amounted to a cost of US$ 1546.3 per person successfully completing the intensive phase of treatment (range US$ 833.8 – US$ 2764.1). This compares to a total cost of US$ 21,875.6 for treating 32 patients in the community, equating to a cost of US$ 729.2 per person successfully completing the intensive phase of treatment (range US$ 341.5 – US$ 1589.1). The cost saved per person successfully completing the intensive phase of TB retreatment was therefore US$ 817.1.

If the unknown user costs were replaced with minimum values, cost per patient was US$ 1505.0 in the hospital arm and US$ 720.8 in the community arm. If these values were replaced with maximum values, cost per patient was US$ 1668.4 v US$ 760.8.

Table 46. Cost-effectiveness of community-based care in the intensive phase of TB retreatment

	Hospital-based management n = 33	**Community-based management n = 32**
Cost indicators		
Total cost 2014 US $	47,936.6	21,875.6
Effectiveness indicators		
Number of patients completing intensive phase retreatment	31	30
Cost-effectiveness indicators		
Cost per patient completing intensive phase retreatment 2014 US$ *	1546.3 (833.8-2764.1)	729.2 (341.5-1589.1)
Incremental cost-effectiveness ratio		
Cost per patient completing intensive phase retreatment 2014 US$	- 817.1	

* Mean cost & range

6.4.2 Health-related quality of life

Health-related quality of life scores at the end of the intervention period for both groups are shown in table 47. There were no significant differences in patient's overall EQ-5D scores, or in individual components of the score, between the two groups. The change in EQ-5D score from baseline was similar in both groups. There was also no difference in VAS scores between patients managed in the community and those managed in the hospital. Overall, VAS scores were higher than EQ-5D scores, but the two scores were well correlated (Pearson correlation coefficient 0.66).

Table 47. Health-related quality of life scores at the end of the intensive phase of TB retreatment

	Total population n = 182 (%)	Hospital-based management n = 89 (%)	Community-based management n = 93 (%)	p-value*
Effectiveness indicators				
EQ-5D: Utility score	0.884	0.889	0.880	0.80
EQ-5D: Problems with mobility	19/172 (11.1)	9/85 (10.6)	10/86 (11.6)	1.00
EQ-5D: Problems with self-care	6/172 (3.5)	5/85 (5.9)	1/86 (1.2)	0.12
EQ-5D: Problems with usual activities	18/172 (10.5)	12/85 (14.1)	6/86 (7.0)	0.14
EQ-5D: Problems with pain	25/171 (14.6)	13/85 (15.3)	12/86 (14.0)	0.83
EQ-5D: Problems with anxiety	16/172 (9.3)	9/85 (10.6)	6/86 (7.0)	0.43
Change in EQ-5D from baseline	0.04	0.01	0.07	0.11
VAS score	96.7	96.1	97.3	0.23

* Bootstrapped estimates of mean difference for continuous variables; Fishers exact test for categorical variables

6.4.3 Costs and outcomes of TB retreatment at 8 months

User costs during continuation phase of retreatment

Data on costs after completing the 8 month course of TB retreatment were available for 122 study participants. There was no significant difference in the overall costs incurred by users after the intensive phase of treatment, with a mean difference of US$ 36.2 (US$ -28.5 - US$ 100.9) (table 48).

Table 48. User costs during the continuation phase of TB retreatment

	Mean cost US dollars (95%CI)		
	Hospital-based management	**Community-based management**	**Mean difference***
Patient costs			
Direct medical & non-medical			
Re-admission	5.3 (-0.8-11.4)	11.0 (2.6-19.5)	-5.7 (-16.1-4.6)
Visits to TB office	33.4 (16.2-50.7)	27.1 (19.3-35.0)	6.3 (-12.4-25.0)
Visits to ARV clinic	26.5 (-6.0-58.9)	8.3 (5.3-11.4)	18.1 (-14.2-50.5)
Visits to health centre	0.4 (0.0-0.7)	1.4 (-0.1-3.0)	-1.1 (-2.6-0.5)
Visits to hospital OPD	5.5 (-4.9-15.9)	0.7 (-0.3-1.6)	4.8 (-5.2-14.9)
Indirect costs	8.6 (5.9-11.3)	14.0 (7.3-20.7)	-5.4 (-12.4-1.6)
TOTAL PATIENT COSTS	79.7 (30.7-128.6)	62.6 (44.9-80.3)	17.1 (-35.1-69.2)
Guardian costs			
Direct medical & non-medical			
Re-admission	16.7 (0.8-32.6)	5.3 (-0.5-11.2)	11.4 (-5.4-28.2)
Visits to TB office	4.4 (0.1-8.8)	6.2 (-.08-13.2)	-1.7 (-9.7-6.1)
Visits to ARV clinic	1.8 (-0.3-3.9)	0.6 (0.0-1.2)	1.2 (-0.9-3.3)
Visits to health centre	0.2 (-0.1-0.4)	0.4 (-0.2-1.0)	-0.2 (-0.9-0.4)
Visits to hospital OPD	5.3 (-5.1-15.7)	0.5 (-0.5-1.4)	4.9 (-5.2-15.0)
Indirect costs	5.4 (-0.2-11.1)	1.7 (0.8-2.7)	3.7 (-1.8-9.2)
TOTAL GUARDIAN COSTS	33.9 (9.6-58.2)	14.8 (2.1-27.4)	19.2 (-7.5-45.8)
TOTAL USER COSTS	**113.6 (55.3-171.9)**	**77.4 (48.6-106.1)**	**36.2 (-28.5-100.9)**

* Bootstrapped estimates of mean difference and 95% CI

Health care usage during continuation phase of retreatment

Eleven patients were readmitted after completing streptomycin injections – 8/63 (12.7%) in the community arm and 3/59 in the hospital arm (5.1%) (Risk Ratio 2.50, 95%CI 0.70-8.97; p-value 0.21). The mean number of admission days during the continuation phase for patients in the hospital arm was 1.32 (95% CI -0.75-3.39), compared a mean number of admission days in the community arm of 2.49 (95%CI 0.05-4.93) (t-test p-value 0.47). There were no significant differences in the number of visits to the TB office, health centre or hospital outpatient department (table 49). There is a suggestion that patients who had been managed in hospital attended ARV clinic more often than those who had been managed in the community (mean number of visits 3.61 v 2.81, p-value 0.08).

Table 49. Mean number of contacts with health facilities during the continuation phase of TB retreatment

	Hospital-based management	Community-based management	p-value*
Readmission	5.1	12.7	0.21
TB office	5.24	5.24	0.99
ARV clinic	3.61	2.81	0.08
Health centre	0.26	0.41	0.48
Hospital OPD	0.18	0.17	0.96

* Student t-test

6.4.4 Catastrophic costs and dissaving

6.4.4.1 Factors associated with incurring catastrophic household costs

During the first two months of TB retreatment, 109/180 (60.6%) patients experienced health costs of ≥10% annual household income, and 67/180 (37.2%) experienced costs of ≥20% annual household income (table 50). In univariate analysis, being HIV positive was associated with increased odds of catastrophic costs at both the ≥10% and ≥20% thresholds. After controlling for age, gender, residence and wealth, HIV remained significantly associated with catastrophic costs.

Table 50. Catastrophic costs during the intensive phase of retreatment

	Catastrophic cost	p-value	OR	p-value	aOR *
Cost ≥10% annual HH income					
Age group					
<30	25.44 (56.8)				
30-35	27/40 (67.5)	0.32	1.58 (0.6503.84)	0.53	1.36 (0.52-3.57)
36-45	39/61 (63.9)	0.46	1.35 (0.61-2.98)	0.99	0.99 (0.42-2.37)
>45	18/35 (51.4)	0.63	.080 (0.33-1.96)	0.40	0.65 (0.25-1.74)
Gender					
Male	72/127 (56.7)				
Female	37/53 (69.8)	0.10	1.77 (0.90-1.50)	0.28	1.50 (0.72-3.12)
HIV status					
Negative	13/35 (37.1)				
Positive	96/145 (66.2)	0.002	3.32 (1.54-7.14)	0.01	3.01 (1.25-7.24)
Residence					
Urban	97/158(61.4)				
Rural	11/20 (55.0)	0.58	0.77 (0.30-1.96)	0.95	1.05 (0.28-3.95)
Wealth quartile					
First	21/41 (51.2)				
Second	31.45 (68.9)	0.10	2.11 (0.88-5.08)	0.08	2.27 (0.91-5.70)
Third	28/46 (60.9)	0.37	1.48 (0.63-3.47)	0.41	1.46 (0.60-3.53)
Fourth	27/44 (61.4)	0.35	1.51 (0.64-3.58)	0.34	1.70 (0.60-4.99)
Cost ≥20% annual HH income					
Age group					
<30	13/44 (29.6)				
30-35	18/40 (45.0)	0.15	1.95 (0.79-4.79)	0.26	1.73 (0.66-4.52)
36-45	23/61 (37.7)	0.39	1.44 (0.63-3.31)	0.92	1.05 (0.43-2.58)
>45	13/35 (37.1)	0.48	1.41 (0.55-3.62)	0.61	1.30 (0.48-3.55)
Gender					
Male	42/127 (33.1)				
Female	25/53 (47.2)	0.08	1.81 (0.94-3.47)	0.16	1.64 (0.82-3.27)
HIV status					
Negative	7/35 (20.0)				
Positive	60/145 (41.4)	0.02	2.82 (1.16-6.89)	0.04	2.79 (1.03-7.57)
Residence					
Urban	59/158 (37.3)				
Rural	8/20 (40.0)	0.82	1.12 (0.43-2.90)	0.18	2.53 (0.66-9.72)
Wealth quartile					
First	13/41 (31.7)				
Second	17/45 (37.8)	0.56	1.31 (0.54-3.19)	0.56	1.32 (0.52-3.13)
Third	22/46 (47.8)	0.13	1.97 (0.82-4.74)	0.81	2.02 (0.81-5.01)
Fourth	15/44 (34.1)	0.82	1.11 (0.45-1.76)	0.26	0.80 (0.26-2.46)

** Adjusted for age, gender, HIV, residence and wealth*

Table 51 Mean key costs for HIV positive and HIV negative patients

	HIV negative	HIV positive	Mean difference*
Patient food	35.52 (23.41-47.64)	51.6 (43.43-59.68)	16.03 (1.93-30.13)
Guardian food	12.21 (3.58-20.85)	16.51 (12.09-20.94)	4.30 (-5.10-13.80)
Patient lost earning	46.68 (25.93-67.42)	95.38 (79.48 -111.27)	48.70 (21.81-75.59)
Guardian lost earning	7.89 (2.22-13.57)	14.25 (6.43-22.07)	6.36 (-3.15-15.86)

* Bootstrapped estimates of mean difference and 95% CI

The predominant costs for HIV positive and HIV negative patients are shown in table 51. Patients who were HIV positive spent significantly more on food (mean difference US$ 16.03) and lost significantly more earnings (mean difference US$ 48.7).

6.4.4.2 Association between care delivery method and catastrophic household costs

Significantly fewer households incurred costs of ≥10% or ≥20% annual household income if patients received community-based care (tables 52 and 53). Community based care reduced the risk of incurring costs of ≥10% annual household income by 60%. The risk of incurring costs of ≥20% annual household income was reduced even further (by 84%) in the group who received community-based care. As demonstrated by the stratified analyses, the effect of community-based care in reducing catastrophic costs was independent of the wealth status of the household, gender and HIV status of the patient.

Table 52. Risk of incurring costs of ≥10% of household income according to study arm

	Total population	Hospital-based management	Community-based management	Risk Ratio
All participants	109/180 (60.6)	79/92 (85.9)	30/88 (34.1)	0.40 (0.29-0.54)
Wealth quartile				
First	21/41 (51.2)	17/19 (89.5)	4/22 (18.2)	0.20 (0.08-0.50)
Second	31/45 (68.9)	22/26 (84.6)	9/20 (45.0)	0.53 (0.32-0.89)
Third	28/46 (60.9))	20/25 (80.0)	8/21 (38.1)	0.48 (0.27-0.85)
Fourth	27/44 (64.3)	20/23 (87.0)	7/21 (33.3)	0.38 (0.21-0.72)
Gender				
Male	72/127 (56.7)	50/60 (83.3)	22/67 (32.8)	0.39 (0.27-0.57)
Female	37/53 (69.8)	29/32 (90.6)	8/21 (38.1)	0.42 (0.24-0.73)
HIV status				
Negative	13/35 (37.1)	9/12 (75.0)	4/23 (17.4)	0.23 (0.09-0.60)
Positive	96/145 (66.2)	70/80 (87.5)	26/65 (40.0)	0.46 (0.34-0.62)

Table 53. Risk of incurring costs of ≥20% household income according to study arm

	Total study population	Hospital-based management	Community-based management	Risk Ratio
All participants	67/180 (37.2)	58/92 (62.0)	9/88 (11.4)	0.16 (0.08-0.41)
Wealth quartile				
First	13/41 (31.2)	13/19 (68.4)	0/22 (0.0)	NA
Second	17/45 (37.8)	14/26 (53.9)	2/20 (10.0)	0.17 (0.04-0.64)
Third	22/46 (47.8)	16/25 (64.4)	6/21 (28.6)	0.45 (0.20-0.93)
Fourth	15/44 (34.1)	14/23 (60.1)	1/21 (4.8)	0.07 (0.01-0.54)
Gender				
Male	42/127 (33.1)	36/60 (60.0)	6/67 (9.0)	0.15 (0.07-0.33)
Female	25/53 (47.2)	22/32 (68.8)	3/21 (14.3)	0.21 (0.07-0.61)
HIV status				
Negative	7/35 (20.0)	7/12 (58.3)	0/23 (0.0)	NA
Positive	60/145 (41.4)	51/80 (63.8)	9/65 (13.9)	0.22 (0.12-0.41)

6.4.4.3 Association between catastrophic costs and treatment outcome

In univariate analysis, catastrophic costs were significantly associated with an increased risk of unsuccessful treatment outcome if catastrophic costs were defined as costs of ≥20% annual household income, but the association was weaker if they were defined as ≥10% of annual household income (table 54). After controlling for age, gender, wealth and HIV, the odds ratio for unsuccessful treatment outcome comparing households which incurred costs of ≥20% annual household income to those which did not was 2.74 (95% CI 1.06-67.08; p-value 0.04). A multivariate logistic regression model which included an interaction term between wealth quartile and costs ≥20% annual household income demonstrated that wealth quartile did not modify the effect of catastrophic cost on 8 month treatment outcome. The odds of unsuccessful treatment outcome were higher in those who incurred costs ≥20% annual household income, regardless of study arm, although confidence intervals around the estimates became wide (OR in community arm 3.43 (95% CI 0.52-22.80); OR in hospital arm 3.50 (95% CI 0.68-17.91); Wald p-value for interaction 0.988).

Table 54. Association of catastrophic cost with clinical outcome

	Unsuccessful outcome	p-value	OR	p-value	aOR*
Cost ≥10% annual HH income					
No	6/57 (10.5)				
Yes	18/80 (22.5)	0.08	2.47 (0.91-6.68)	0.08	2.52 (0.89-7.17)
Cost ≥20% annual HH income					
No	10/84 (11.9)				
Yes	14/53 (26.4)	0.03	2.66 (1.08-6.53)	0.04	2.74 (1.06-7.08)

** Adjusted for age, gender, wealth and HIV status*

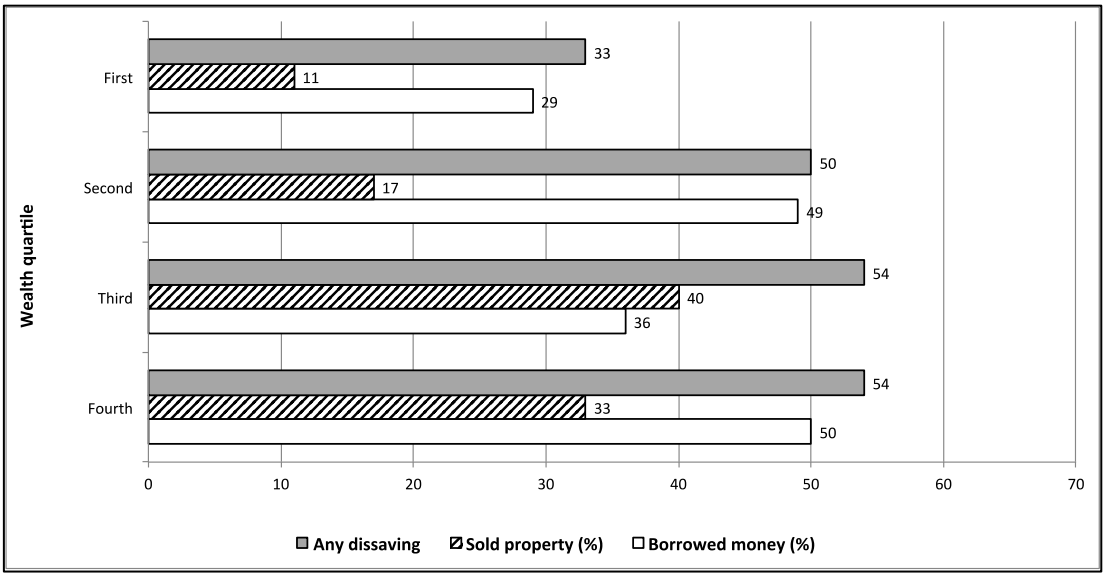
6.4.4.4 Dissaving

Overall, 77/187 (41.2%) households borrowed money to cover the costs of healthcare (table 55). Most commonly, money was borrowed from a friend/neighbour (48/77, 62%) or family member (22/77, 29%). Participants also took loans from employers (2), banks (2), a friend or relative's employer (1) and other sources (2). There was no difference between participants in the two study arms in terms of the amount of money they borrowed or were required to repay. In the study population as a whole, 26% of households sold property in order to cover the costs of health care, usually a household item. The proportion of participants who sold property and the pattern of what was sold did not differ by study arm.

Table 55. Dissaving during the intensive phase of retreatment according to study arm

	Total study population	Hospital-based management	Community-based management	p-value
Borrowed money	77/187 (41.2)	39/94 (41.5)	38/93 (40.9)	1.00
Amount borrowed (mean US$)	12.2	10.6	14.1	0.52
Amount repaid (mean US$)	12.5	10.3	15.0	0.39
Sold property	48/185 (26.0)	23/92 (25.0)	25/93 (26.9)	1.00
Land	1/48 (2.1)	1/23 (4.4)	0/25 (0.0)	0.13
Livestock	4/48 (8.3)	4/23 (17.4)	0/25 (0.0)	
Bicycle or vehicle	1/48 (2.1)	0/23 (0.0)	1/25 (4.0)	
Household item	33/48 (68.8)	15/23 (65.2)	18/25 (72.0)	
Farm Produce	7/48 (14.6)	2/23 (8.7)	5/25 (25.0)	
Other	2/48 (4.2)	1/23 (4.4)	1/25 (4.0)	

Figure 35. Dissaving according to wealth



The proportion of participants who employed any dissaving measure was lower in the first wealth quartile compared to all other quartiles (33% v 52%; RR 1.6, 95% CI 1.04-2.56; p-value 0.02) (figure 35). In all quartiles of wealth apart from the second, participants were more likely to borrow money than to sell property. Overall, 13.7% of participants had to sell property *and* borrow money, with participants in the first wealth quartile less likely than others to both sell and borrow (4% v 17%; RR 0.24, 95% CI 0.06-0.99; p-value 0.03). Unlike catastrophic costs, dissaving was not associated with treatment outcome (table 56).

Table 56. Association between dissaving and clinical outcome

	Unsuccessful outcome (%)	p-value	OR
Any dissaving			
No	12/56 (21.4)	0.32	0.64 (0.26-1.55)
Yes	12/81 (14.8)		
Borrowed money			
No	13/69 (18.8)	0.68	1.2 (0.50-2.91)
Yes	11/68 (16.2)		
Sold property			
No	16/97 (16.5)	0.83	0.90 (0.34-2.40)
Yes	7/39 (18.0)		

Dissaving was not associated with costs of ≥10% annual household income (table 57). Households which experienced costs of ≥20% annual household income were more likely to borrow money and to sell property (table 58), although neither of these associations were statistically significant.

Table 57. Associations between dissaving and costs ≥10% annual household income

	Costs ≥10% annual household income (%)	p-value	Risk Ratio
Borrowed money			
No	61/103 (59.2)	0.61	1.06 (0.84-1.34)
Yes	46/73 (63.0)		
Sold property			
No	80/129 (62.0)	0.45	0.90 (0.67-1.20)
Yes	25/45 (56.3)		

Table 58. Associations between dissaving and costs ≥20% annual household income

	Costs ≥20% annual household income (%)	p-value	Risk Ratio
Borrowed money			
No	35/103 (34.0)	0.19	1.29 (0.89-1.88)
Yes	32/73 (43.8)		
Sold property			
No	44/129 (34.1)	0.14	1.37 (0.92-2.03)
Yes	24/45 (46.7)		

6.5 Discussion

This economic evaluation has demonstrated that community-based management during the intensive phase of TB retreatment is highly cost effective, with large cost savings for both providers and users. Community-based management significantly reduced the risk of catastrophic household expenditure on health, irrespective of wealth, HIV status or gender.

6.5.1 Trial-based economic evaluation

The total cost per patient successfully completing the intensive phase of TB retreatment was US$ 817.1 less for community-based management than hospital based management. Hospital-based management cost on average US$ 1546.3 (95% CI US$ 833.8 - US$ 2764.1) per person, whereas community-based management cost on average US$ 729.2 (US$ 341.5 - US$ 1589.1) per person. Provider costs accounted for the majority of the total costs (US$ 1100.3 for hospital-based care and US$ 498.0 for community-based care), and in both groups ward stay costs made up the bulk of the health-system costs. This highlights the fact that it is the cost associated with the day-to-day running a TB ward which impacts most on the cost of providing treatment, and is a strong argument in favour of moving care away from in-patient facilities. The finding that community-based models of delivering TB care are cost-effective is not new [278-280], and guidelines for the management of new patients [24] and patients on treatment for MDR-TB [26] both advocate community-based care based largely on this fact. However, the cost of managing patients on retreatment regimen has not specifically been addressed until now either in research or in practice recommendations.

Aside from the expenses associated with periods of ward admission, the largest health system costs of community-based management were ART and TB drugs, which are not impacted by the intervention. The mean costs of additional staff time and overheads required for community-based management made up only a small proportion of the total cost of the intervention – the mean cost of staff time being US$ 17.9, transport US$ 7.4 and overheads US$ 6.3 during the entire period.

Although provider costs made up the majority of the total costs, the impact of the intervention on user costs was dramatic. Community-based care reduced user costs by a mean of US$ 169.8 (US$ 128.9 – US$ 210.7). The greatest saving for patients was the reduction in lost earning, indicating that in this cohort of well patients on treatment it was possible for many to return to work once discharged from hospital. This is in keeping with a recent review by Tanimura et al which demonstrated that lost income accounted for 60% (16% - 94%) of patient costs during TB treatment in low and middle income countries [33]. The other large benefit was seen in the lower cost of food for patients managed at home. These findings are in keeping with previous literature which report descriptions of having to provide 'special food' for patients who are sick as well as the increased expense of not being able to feed the whole household from a communal pot [436, 437]. The issues around costs of food are also supported by the accounts of patients in the qualitative evaluation of this intervention (chapter 7) in which having to provide food for patients in hospital is a key theme.

The amount spent by users increased significantly with increasing wealth quartile, suggesting that households spend as much as they possibly can afford to on health, stretching their financial capacity to the limit, a feature which has been described in other studies [431]. It is worth noting that participants who fell into the 'richest' wealth quartile still only had a mean monthly household income of US$ 134.3 and even in the 'rich' group there was still a household with an earth floor. This implies that although there was a spectrum of wealth amongst study participants, this spectrum was fairly narrow and most households were still relatively poor.

6.5.2 Catastrophic household costs

The huge reduction in absolute costs seen in those who received community-based management translated to a significant impact on catastrophic household costs. In the cohort as a whole, 60.6% of participants experienced health costs of ≥10% annual household income and 37.2% experienced health costs of ≥20% annual household income. After adjusting for age, gender, HIV, residence and wealth

quartile, only being HIV positive was significantly associated with incurring catastrophic costs. Factors which contributed to the increased costs for HIV positive patients were higher expenditure on food and greater lost earnings. The higher degree of lost earnings may be partly explained by the fact that the HIV positive group on average earned more than the HIV negative group prior to starting treatment (US$ 16.95 v US$ 11.89 per week). Spending more money on food might also have reflected the fact that HIV positive patients had more money available, however total annual incomes were comparable between households in which the patient was HIV positive (US$ 1322) and those in which the patient was HIV negative (US$ 1323). Instead, it is possible that families of patients who were HIV positive recognised the importance of nutrition, for example having been through counselling in ART facilities, and therefore prioritised providing good quality food for patients, or that HIV positive patients were more obviously malnourished and in need of feeding.

It is surprising that catastrophic health costs were not associated with wealth quartile, as a number of studies have shown that health expenditure affects the poorest in society the most [5, 33, 436]. A possible reason for the different finding in the current study is that health spending increased with wealth, suggesting that households in this setting will spend maximally on looking after a sick member of the household – whatever is available will go to ensuring care for the patient. More importantly, as has already been discussed, the cohort as a whole was very poor with little difference in the income between 'richest' and 'poorest'. It is likely that a large number in even the 'richest' quartile in this study would have been classified as 'poor' in many other settings.

The effects of catastrophic expenditure associated with TB treatment go beyond the immediate effects of driving households into poverty. Poverty is well known to be a risk factor for the development TB [29], delayed TB diagnosis [438] and poor adherence [293, 439]. If accessing TB care drives people even further into financial hardship, a vicious cycle is established in which families and communities are put at ever increasing risk of both TB and worsening poverty. Moreover, catastrophic

health costs have now been shown to correlate with clinical outcomes for patients on TB treatment [275]. This recent paper by Wingfield et al has demonstrated that catastrophic cost, defined at a threshold of ≥20% annual household income (but not at thresholds of ≥10% or ≥15%) was independently associated with poor clinical outcome. That finding has been replicated by this study: expenditure of ≥20% annual household income was associated with an adjusted odds ratio for adverse clinical outcome of 2.74 (1.06-7.08), but the association at a threshold of ≥10% was not statistically significant. A key feature of both the Wingfield paper and this study is that they recognise the contribution of direct non-medical costs and lost earnings. This is particularly important in settings where TB care is provided free and therefore to only focus on direct medical costs would be misleading and underestimate the financial impact of illness on households. The association between catastrophic cost and clinical outcome can be explained by a number of possible mechanisms including inadequate nutrition; more severe disease; and poorer adherence due to barriers in meeting costs of accessing health care during treatment.

The serious consequences of catastrophic health expenditures are increasingly being highlighted. The WHO post-2015 Global TB Strategy emphasises that without both universal health coverage and social protection, improvements in TB care and prevention will not be possible. As such, one of the targets of the post-2015 strategy is that “no TB affected families should experience catastrophic costs due to TB” [276]. Over recent years, strategies promoted in order to reduce catastrophic health costs have included universal health coverage (UHC), defined as “universal access to needed health services without financial hardship in paying for them”; as well as various social protection measures aiming to mitigate the effects of poverty associated with accessing health care [440]. Social protection measures evaluated in tuberculosis have included health insurance schemes, food assistance, cash transfers and micro-finance schemes [441, 442]. After a successful piloting phase, an exciting socioeconomic intervention to enhance TB control in Peru through a combination of conditional cash transfers and social support is currently being

evaluated and is showing great promise in reducing catastrophic costs and improving retention in care [443].

This study has shown that community-based management during the intensive phase of retreatment reduced the risk of incurring costs ≥10% annual household income by 60%, and the risk of incurring costs ≥20% annual household income by 84%. Of participants who received community-based management, only 11.4% experienced health costs of ≥20% annual household income, compared to 62.0% of patients managed in the hospital. This intervention therefore offers an alternative model of care for patients on TB retreatment which significantly reduces the risks of catastrophic household costs.

It is possible that community-based management has varying impact on catastrophic health expenditure for different groups within the population. If this were the case, the intervention may address some of the issues surrounding equitable access to healthcare, and as such it was important to examine the effect of the intervention in key groups. The data clearly show a reduction in the risk of incurring catastrophic costs which is independent of wealth quartile, gender and HIV status, and these benefits were seen at the thresholds of both 10% and 20% annual household income. As the overall risk of experiencing catastrophic costs was the same across these groups, it is useful to also know that the intervention is effective in reducing the risk for all groups.

6.5.3 Dissaving

A large proportion of participants employed dissaving measures such as borrowing money (41.2%) or selling property (26.0%), most commonly a household item, which is a common finding [444]. These data are corroborated by descriptions of coping mechanisms seen in the qualitative evaluation of the intervention, in which it is seen that having to borrow money caused particular distress. Participants who fell into the least poor quartile were less likely to employ dissaving measures than other participants. This is an interesting finding because it indicates that the richest

quartile in this population are willing spend a proportion of their disposable income on health which is similar to all other participants, but unlike the poorer participants this amount is sufficient to cover the costs of illness without having to sell or borrow. Unlike catastrophic costs, dissaving was not associated with clinical TB outcome.

As addressing the problems of catastrophic costs is moving up the health policy agenda, it will become more important to define and to measure them. Currently, determining user costs involves long and sometimes complex participant interviews [426], which are poorly standardised. If instead a simple indicator could be used to screen for catastrophic expenditure, it would allow for better comparisons and possibly mean that an assessment of catastrophic costs could be incorporated into the routine holistic management of people with TB. It is for this reason that the associations between household expenditure and dissaving were evaluated. At a 10% threshold for defining catastrophic cost, there was no association between catastrophic cost and dissaving. At a 20% threshold however, more patients who borrowed money (43.8% v 34.0%) and who sold property (46.7% v 34.1%) experienced catastrophic costs, although these differences were not significant. Nevertheless, this is an interesting area which deserves further evaluation with larger populations.

6.5.4 Health related quality of life

Quality of life scores at the end of the intensive phase of retreatment were the same in both groups. This is in line with other functional measures that were evaluated (Karnofsky score and SRQ) which were also very high in both groups throughout the study. These findings are unsurprising because the study selected a sub-group of very well patients, as the protocol determined they all had to be clinically well enough to no longer require hospital admission. The modalities in which patients most frequently experienced problems were pain (14.6%), mobility (11.1%) and carrying out usual daily activities (10.5%). Given that these patients had all recently had a diagnosis of TB, it is not surprising that these are the areas of their

lives which were most affected. Overall, VAS scores were higher than EQ-5D questionnaire utility scores, which is a common finding.

6.5.5 Costs and outcomes during the continuation phase of retreatment

During the continuation phase of treatment, the costs to participants were comparable between those who had received community-based and hospital-based care during the intensive phase (mean difference US$ 36.2, 95% CI -28.5-100.9). There were no significant differences in the number of contacts with health facilities during the continuation phase of treatment, and there was no difference in overall treatment outcomes at 8 months. As both costs and healthcare usage were similar in the two groups, it is likely that there was no major increase in the long term cost of community-based care compared to hospital-based care.

6.5.6 Study limitations

A limitation of this study is the fact that user costs were not available for the patients who did not complete the intensive phase. It was not felt to be appropriate to question guardians about costs soon after a patient had died, and data were not available for those patients who had defaulted. It is quite possible that the costs incurred by patients who did not complete the intervention were different from those who did, however a sensitivity analysis using high and low costs did not meaningfully alter the estimate of total costs. Another weakness is that opportunity costs for patients and guardians who had no regular income were not estimated. This is a common problem in performing health economic evaluations, particularly in low income countries where a large proportion of study participants have no regular income, and particularly for women who are generally less likely to have formal employment. Alternative approaches include substituting the average cost of the lowest wealth quartile in the study population; estimating a value based on national survey data (e.g. Demographic Health Survey); or using total income rather than earning. It is worth noting that all consumables used as part of community-based care such as needles and syringes were accounted for in the provider costs of

the intervention. This will have slightly over estimated the cost of community-based care as these will also have been included in the running costs of the ward. However, it was thought to be important that *all* the costs of the intervention were clearly presented. Finally, the inability to perform a formal assessment of provider costs at 8 months is also a limitation of this evaluation. It must be recognised that user costs were only estimated for the period after the start of TB treatment, as the costs associated with diagnosis were assumed to be the same in both arms of the trial. However, it is well recognised that a significant proportion of patient costs are incurred during the process of obtaining a diagnosis of TB, before treatment is started [274, 437, 445]. It cannot be claimed that the intervention would have any effect on reducing the pre-diagnosis costs, and therefore if total costs including all those from onset of symptoms until the end of treatment were included in this analysis, the overall difference in costs between the two study arms may have be lower.

6.6 Conclusion

Patients on retreatment only make up a small proportion of the total number of all patients treated for TB. However, the current necessity for in-patient care, and the association between hospital-based management and extremely high risks of catastrophic health expenditure mean that this group of patients deserve special attention if the post-2015 target of "no families experiencing catastrophic costs" is to be reached. This evaluation has demonstrated that community-based management during the intensive phase of retreatment is cost effective for both providers and users, and that the financial benefits to households of community-based care are seen across a spectrum of patients. Additionally, the study has contributed to the body of evidence showing that catastrophic health costs are associated with clinical outcomes on treatment, and that in order to improve TB care, interventions are required to reduce the economic hardships suffered by households as a result of illness.

7 Qualitative Evaluation of the TB-RROC Trial

7.1 Introduction

This chapter evaluates the TB-RROC intervention from a qualitative perspective. It aims to describe the experiences of people affected by recurrent TB, including patients, guardians, household members, and healthcare workers. Using qualitative methods allows for in-depth exploration of the context in which treatment is delivered and the opportunity is taken to explore how participants' circumstances influence their experiences. Particular attention is therefore paid to participants' pre-existing personal, social and financial situations, and how these factors impact on their experiences of treatment. The conditions in which care for patients with recurrent TB is currently delivered are also examined, before going on to explore the experiences of participants who received community-based management as part of the TB-RROC trial and evaluating the mechanisms by which community-based management may affect care in different situations.

7.1.1 Methodological perspectives in qualitative research

Research is framed within a number of distinct paradigms. The ontological and epistemological beliefs of an investigator will determine their approach to a research question, therefore the paradigm within which a study is conducted influences it's design, implementation and analysis [446, 447]. The TB-RROC study was conducted from a realist perspective (see chapter 2), employing a combination of methodologies to inform a broad evaluation of the intervention [446, 448]. In keeping with this framework and considering the research question of interest, the qualitative evaluation used phenomenography – a method for examination of the 'lived experience' [449].

Phenomenography

The word 'phenomenon' originates from the Greek *phainonenon*, meaning 'a thing appearing to view', and can be defined as a 'fact or situation that is perceived or observed to exist'. *Phenomenography*, a qualitative research methodology, must be differentiated from *phenomenology*, a philosophical theory [450]. Although both aim to examine human experience and awareness of phenomena, phenomenography is a research approach which aims to describe the different ways a group of people understand a phenomenon, whereas phenomenology aims to clarify the structure and meaning of a particular phenomenon [451].

Phenomenography was first developed as a methodological approach to qualitative research by a group of Swedish researchers in the 1970s, and is particularly associated with Ference Marton who describes it as "research which aims at description, analysis and understanding of experiences" [452]. Rather than focusing on the phenomenon itself and aiming to uncover the singular essence of that phenomenon, the emphasis in phenomenography is on the variation in the way people understand a given phenomenon. Conventional research is often described as 'first order', where the perspective is 'from the outside' and describes people and the world they experience in broadly the same way. However, phenomenography adopts a 'second order', or 'from the inside' perspective as it attempts to understand the world from the perspective of the subjects being studied [449].

A phenomenon can be experienced in an infinite number of different ways, and this experience is a product of the interaction between the subject and the phenomenon itself. Therefore, in phenomenography, analysis compares data obtained from a particular group of people and leads to the identification of different interpretations, known as 'categories of description' [451, 452]. These refer to descriptions of the various ways in which the phenomenon *can* be understood at a collective level, and together form the 'outcome space'. Categories of description are usually related to each other, so that higher level analysis

examines the structures and interactions between categories within the outcome space [453].

Interviewing and Thematic Content analysis

Interviewing is the most commonly used tool for data collection in phenomenographic studies [454]. As the aim of research is to understand the variation in participant experience and understanding, a broad range of subjects are sampled in order to obtain data not just about the most common experiences, but to ensure many different perspectives are represented [449]. In depth interviews are conducted in which the interviewer sets the topic and guides discussion around the phenomenon of interest, but the participant is able to control the agenda and determine which information they provide. The aim is to encourage the participant to speak freely of their experiences and to gather data that represent the participants' own understanding [455, 456]. This technique is in keeping with the realist approach, where by theories are developed by the researcher, and then tested through interviews with study participants [301].

Thematic content analysis (TCA) is not a specific method for conducting qualitative research, but rather a tool for the inductive analysis of data which is systematic and transparent [457, 458]. According to Attride-Sterling it is: "simply a way of organising a thematic analysis of qualitative data… as such, thematic networks analysis is not in any way a new method, but one that shares the key features of any hermeneutic analysis… it makes explicit the procedures that may be employed in going from text to interpretation." She outlines six specific steps in content analysis: (i) code material, (ii) identify themes, (iii) construct thematic networks, (iv) describe and explore thematic networks, (v) summarise thematic networks, and (vi) interpret patterns [459]. By allowing the organisation and description of the data, Thematic Content Analysis facilitates the inductive analysis of data at descriptive and 'higher' network levels; it is therefore an appropriate choice of analysis tool for phenomenographic studies. It is crucial to recognise that in both the collection and

analysis of qualitative transcripts, there is always a degree of subjectivity on the part of the researcher, and there may be multiple interpretations of a text [460].

7.1.2 TB-RROC qualitative analysis

The TB-RROC trial was conceived because it had been recognised that there were many potential disadvantages of hospital-based management during TB retreatment, which may be alleviated by community-based care. It introduced an entirely new method of delivering care by training guardians to do injections at home. The success or failure of a new approach such as this cannot simply be judged on the numeric efficacy outcomes of the trial, but must be interpreted in the light of the experiences of those involved. An understanding of the perspectives of those affected by the new intervention could help to identify whether the approach is acceptable to users, the community, and the health service; to adapt the intervention to maximise it's potential benefit; and to improve it's eventual implementation.

7.2 Research questions

This study aimed to answer two research questions:

1. What are the experiences of adult patients and their guardians in Malawi during the intensive phase of TB retreatment?

2. How are these experiences affected by an intervention that facilitates community-based management through teaching guardians to deliver daily streptomycin injections at home?

7.3 Conceptual framework

In addition to being based on existing theory and research, construction of the conceptual framework for this study was informed by the researchers own experimental knowledge and exploratory research. It is necessary to acknowledge that the intervention being assessed was devised following the researcher's personal experiences as a physician caring for patients receiving TB retreatment regimen. This experience inevitably plays a role in the development of ideas and theories to explore patient and guardian experiences of treatment. Additionally, the study was conducted after completion of a pilot study to assess the feasibility of the intervention, and some months into trial recruitment. Furthermore, during these initial stages, a community advisory board (CAB) consisting of health care workers, patients, guardians and lay members of the public met on a number of occasions. Hence, the framework also draws from conversations with, and observations of, a variety of people who were likely to have insight into the issues being explored.

Figure 36. Conceptual framework

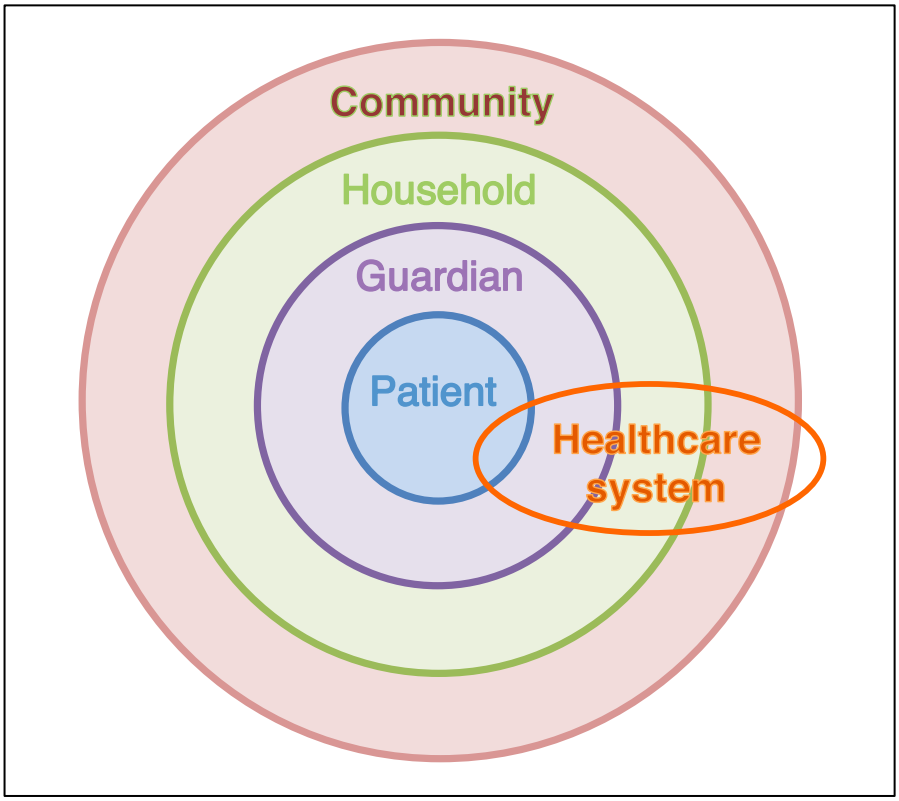


Figure 1 depicts the basis of the conceptual framework. It is recognised that at the centre of the TB treatment event is the patient him or herself, but that the event is experienced not by the patient alone. Closest to the patient is the guardian, who is almost always nested within the household, which itself forms part of the wider community. Not only does TB treatment affect each of these layers independently, it is also important to explore how, if at all, the experience of TB treatment affects inter-relationships between these entities. It is also recognised that an important aspect of TB care, and an aspect which may well be affected by the intervention, is the relationship that patients, guardians, households and the wider community have with healthcare systems, and hence their willingness and ability to engage with health care facilities and interventions. The theoretical basis underpinning this framework and driving the design of the qualitative study is now explored. Many of the issues discussed pertain to the theories about which mechanisms are working in which contexts to influence the experiences of a wide range of study participants, as outlined in chapter 2.

Patient experience

Prolonged hospital admissions have the potential to have profound effects on patients. These effects may be influenced by the reason for the admission, and by the severity of the illness. A proportion of patients admitted to hospital in order to receive TB retreatment are not acutely unwell, and, were it not for the need for daily injections as part of this regimen, many would be managed in the community.

In a systematic review of qualitative research, Munro et al identified factors influencing patients adherence to TB treatment and in so doing described experiences of receiving treatment [293]. A major theme was the financial burden experienced by patients on TB treatment, to the extent that patients felt the need to choose between going to work and attending treatment. The financial costs of TB treatment have been described for both inpatient and outpatient care in a number of settings and are consistently higher for hospitalised patients [279, 281, 461]. In addition to financial consequences, prolonged hospital admissions can have

negative impact on social and psychological well being, including isolation, rejection and boredom [462].

Guardian experience

In many instances, when a patient is admitted to hospital in Malawi their guardian either stays with them in the hospital or visits on an almost daily basis. The effects of hospitalisation can therefore directly impact not only on the patient, but also on their guardian [463]. The experience of guardians is likely to vary substantially, and may be affected by factors such as their relationship to the patient and the gender of both patient and guardian [464].

A concern expressed by the CAB was the potential for the intervention to affect the relationship between patient and guardian. Some members of the board felt that if the patient (usually a man) refused to have an injection, the guardian (usually the wife) would not have the authority to give the injection in the same way a nurse would. Tensions between patients and treatment supporters have previously been described in the realm of TB care – where DOT supporters have been viewed by patients as either constraining or facilitating empowerment [293, 464].

Effects on Households

There exists a body of literature demonstrating the catastrophic effects of illness and hospital admission on the household economic situation of patients, particularly the poor [465]. In previous years, all patients with TB were routinely admitted to hospital for the first two months of treatment, a practice which is no longer standard, in part due to the clear financial burden that this placed on patients and their families [277, 280]. It is important also to recognise that economic costs are not limited to the direct costs of treatment, and that there may be broader socio-economic consequences of illness within a household, for example having to take loans or sell possessions and being unable to send children to school [426].

Capacity to access health care frequently depends on the ability to call upon family members for assistance, and social capital plays a crucial role in this [284]. The strain on households however is not limited to financial and practical hardship - the family is often also a source of emotional and practical support [466].

Community interactions

Data have consistently shown that TB stigma exists within communities and that this can have a profound effect on health seeking behaviour and on patient experience during treatment [200, 467, 468]. Stigma can be defined as 'a mark of disgrace associated with a particular circumstance, quality or person'. It is shaped and perpetuated by institutional and community norms and attitudes, and often results in individuals internalising feelings of shame, disgust and guilt. Two types of stigma have been distinguished: 'enacted' stigma that is external to the person and often concerns discrimination and social inferiority; and 'perceived' or 'internalized' stigma which often arises at least in part from enacted stigma [469]. Within the TB literature, a number of themes recur including fear of infection and transmission; impact on marriage prospects (mainly women) or the ability to provide for a family (mainly men); and the concept that TB is a 'bad disease', which happens to 'bad people' [470, 471].

In more recent years, this issue has been compounded by the 'double stigma' of TB-HIV co-infection, particularly within the context of the HIV epidemic in Sub-Saharan Africa [472-474]. Both qualitative and quantitative evaluations have described that people co-infected with TB and HIV are more likely to have perceived stigma compared to patients not co-infected [475]. Feedback from the TB-RROC CAB has suggested that this stigma is compounded in patients who are being treated for the second or third time for TB. Members of the CAB reported that many people in the Blantyre community believe that multiple episodes of TB is indicative of HIV infection; and that the 2-month admission to hospital in order to receive retreatment regimen makes it hard for patients to keep their diagnosis private. This essentially results in disclosure of both TB and HIV to their community.

Interactions with healthcare services

Some of the effects that TB retreatment in hospital and at home may have on interactions with healthcare services have been touched upon in the previous sections. However, a particular issue that needs further exploration is the specific role that injections (and people who administer injections) play in communities. It has been reported that in low resource settings, injections are frequently purchased without prescription and administered by unqualified people in pharmacies and in market places [476]. This practice is in part driven by beliefs surrounding the benefits of injections, which are viewed a 'strong' form of medication [477, 478]. An important part of the evaluation of the TB-RROC intervention was to assess what the effect was of training lay people to perform injections on community perceptions and expectations of injections and 'injectionists'. Particular attention needed to be paid to whether trained people expected or were expected to administer injections to members of the community other than the patient receiving TB retreatment.

More broadly, the shift of responsibility of care away from the healthcare system to guardians raises the issue of who is responsible for healthcare. Where is the division of responsibility between patients themselves, family and social networks, and health care systems? It has sometimes been seen as the community's role to promote recommended health behaviours, influence social norms regarding health and contribute resources where feasible; whereas the health service is seen as providing human resources, infrastructure, equipment and medications [479]. In recent decades however, the role of community members in delivering or supporting care for patients has been increasing, especially in the field of TB-HIV management [154, 271, 480], which is generally seen as a positive development. However, a concept which is less well explored, is the possibility that task-shifting to family members, particularly a high level responsibility such as administering injections, carries with it more problematic issues for the community. For example, communities may view this as blurring the lines between the duties of healthcare

systems and societal duty, and it may place an undue burden on communities which they believe should remain with formal healthcare structures.

7.4 Methods

7.4.1 Overview of data collection methods

In-depth interviews with trial participants were conducted. This was chosen as the most appropriate data collection method because the experiences of participants were likely to be very personal in nature, both in terms of sensitive medical information and in terms of relationships with others. It was felt that one-to-one interviews would be the environment best suited to allow participants to speak freely and therefore provide the most useful data. Triangulation of the primary data was achieved by conducting a number of key informant interviews as well as observations of patients at home and in the ward. Key informant interviews were done with a range of people including nurses, TB officers, and other members of the community. Although not directly relevant to the research questions, a small number of focus group discussions were held in order to obtain more detailed data about community attitude to guardians providing injections. Overall, the methods were designed to provide a comprehensive assessment, which took account of perspectives from a wide range of people potentially affected by the intervention.

7.4.2 The study team

The study team consisted of six investigators. Each had varying degrees of involvement in the TB-RROC trial and in collection of the primary qualitative data. All had previous research experience in the field of TB and HIV research in Malawi; some but not all were clinically trained; half the team were female; and there was a mixture of Malawian and UK born researchers (see responsibilities table on page v).

MP conducted the primary data collection with support from DC; and DC performed the initial coding with input from MP. DC was the primary investigator on the TB-

RROC trial. She is originally from the UK, but has worked for a number of years as a doctor in the adult medical wards and clinics at QECH. She therefore had personal relationships with a number of the study participants, both as the physician in charge of their medical care, and as the investigator responsible for the study in which they were enrolled. MP is a Malawian born social scientist with extensive experience performing data collection in the field; he had no involvement in the main TB-RROC trial. SBS is a senior clinician and professor at LSTM; he has worked in applied health research in Malawi since the 1990s, and is the overall supervisor of the TB-RROC Study. Other members of the team had no involvement in the trial, but were involved in the design, supervision and analysis of the qualitative evaluation. HB is a Malawi trained clinician with an interest in chronic lung disease and access to health care, and is the Research Manager at the REACH Trust – a multi-disciplinary research NGO based in Lilongwe. ND is a British Medical Anthropologist and Senior Lecturer at LSTM who has worked in Tanzania and Malawi for over a decade in mixed methods applied research and leads the Social Science Programme at MLW. IN is a senior social scientist with an interest in promoting equity in access to health care for the poor, and is Executive Director of the REACH Trust.

7.4.3 In-depth interviews with trial participants

Study population & sampling framework

Study participants had previously been enrolled in the TB-RROC trial at QECH or Bwaila hospital. Purposive sampling of trial participants was employed to ensure that a broad range of perspectives was covered, and that the views of patients and guardians managed both in hospital and in the community were obtained (see table 59). Depending on the sampling framework and willingness to participate, both members of a patient-guardian pair or only one member of the pair were recruited. As described in the conceptual framework, the roles and experiences of both patient and guardian may be affected by gender. This is reflected in the sampling

matrix that aimed to ensure representation of both genders in each role. An attempt was also made to interview at least 2 guardians who cared for patients who either died or had adverse clinical events, because these extreme cases may have different experiences (e.g. feelings of guilt or responsibility) from those who did not experience complications during treatment. Data was collected until it was felt that saturation had been reached and no new concepts were arising. The PI and the research assistant continuously assessed whether saturation had been reached, with input from other co-investigators when necessary.

The trial was conducted in two central hospitals that provide comparable care in similar settings. It was therefore unlikely that the experiences of participants were going to differ vastly between the two sites. It is for this reason that the majority of data collection took place at QECH. However it was also recognised that there may have been some inconsistencies across the two sites, such as cultural diversity (for example the influence of Yao and Chewa traditions[4]), and varying distances between home and hospital. Therefore, a number of interviews were conducted in Bwaila, according to the general sampling framework. Once it was established that there were no new themes emerging from participants in Lilongwe, no further interviews were conducted at that site.

Table 59. Sampling matrix

Patients 20				Guardians 20			
Home 10		Community 10		Home 10		Community 10	
Male 5	Female 5	Male 5	Female 5	Male 5	Female 5	Male 5	Female 5

[4] Both the Chewa and Yao are Bantu tribes of Malawi. Chewa is the largest group in the country, and Chewa society is matrilineal. The Yao are predominantly Muslim and live mainly in the central and southern lakeshore areas. There are a larger number of Yao people living in Lilongwe than in Blantyre.

Recruitment strategy

Patients in the TB-RROC trial were approached as they completed the intervention (i.e. after 2 months of TB treatment). A member of the trial study team initially asked if they would be willing to be interviewed by an independent researcher about their experiences during treatment. If participants agreed to take part, they were introduced to the qualitative research assistant (MP), who was somebody not previously involved in their care or in the trial.

Interview schedule, setting and process

Participants were interviewed individually. They were given a choice whether to be interviewed in their home or at the hospital. This was because some may have preferred the privacy offered by an interview at the healthcare facility, whereas others may have been more comfortable in their own home. If participants chose to be interviewed at the hospital, the interview was conducted in a quiet room close to, but not on, the TB ward at QECH. Interviews were conducted within the first two weeks *after* completing the intensive phase of TB retreatment. This time point was chosen because participants still on intensive phase treatment under the care of the study team may not yet have felt able to talk freely and reflectively about the experience; but it was a time point not too far from the event which should have meant that participants were still able to recall clearly their experiences.

Prior to conducting each interview, basic demographic details were recorded on an anonymised front sheet. All interviews were conducted by a single research assistant (MP) in Chichewa, the local language. A prepared interview guide was designed to answer the research questions within the structure of the conceptual framework and test theories about which mechanisms were operating to generate clinical, social and economic experiences of study participants (appendix 8). The interview guide was adapted iteratively as the study progressed. Interviews were recorded using a digital dictaphone. Following each interview the research assistant

was debriefed by the PI, who systematically compiled field notes based on these discussions.

7.4.4 Key informant interviews

In order to provide further information from a broad range of people who have contact with patients receiving TB retreatment, and to triangulate the data collected from study participants, a number of key informant interviews were conducted. Key informants were selected on the basis of their specific ability to provide information about the experiences of people who may have been affected by the intervention being assessed. Key informants included a variety of health care workers (nurses, TB officers); other members of the community, for example household members who did not directly participate in the study; and patients who declined to participate in the trial. Key informants were asked to provide informed consent. The interviews were conducted at a place and time that was convenient for the participant, ensuring privacy and confidentiality at all times. Participants were interviewed individually with reference to a prepared topic guide (appendix 8). As with the in depth interviews of participants, interviews were recorded using a digital dictaphone and wherever possible following the interview the research assistant and PI had a debriefing interview from which field notes were made.

7.4.5 Observations

The research assistant performed a number of observations of activities during TB retreatment. The purpose of these observations was not only to provide further information in order to add to the triangulation of the data, but also to note any changes in behaviours, attitudes and feelings over time. The RA observed patients behaviours and interactions on the ward; and also accompanied the trial fieldworker on home visits to watch the dynamics and conditions within the households during those visits.

For observations in the community, the research assistant accompanied the fieldworker on the home visit. He was introduced to the participant as a colleague

of the field worker. The study was discussed with the sister in charge of the TB ward prior to doing any observations on the ward. Patients on the ward were not formally introduced to the research assistant who carried out observation, as this would have significantly biased the results. Observations only took place in public places, and therefore did not result in additional breaches of privacy or confidentiality. The research assistant placed himself in an unobtrusive place within the ward in order to carry out his observations, and did not directly interfere with patient care. During these periods of observation, the RA used a field guide (appendix 8) and took field notes, which were later formally written up. After the observations the PI debriefed the RA and made additional notes.

7.4.6 Focus group discussions

It was recognised that the attitude of the community towards guardians providing injections to patients at home not only affects the experience of patients and guardians, but may also play a key role in the potential acceptability of the intervention were it to be rolled out in the future. Therefore, an amendment was added to the initial protocol to do 2 focus group discussions (FGDs) in order to gain more in depth understanding of the response of people in the broader community. Focus groups composed 8-10 people with varying degrees of experience with TB and TB treatment, and included patients who had had TB, guardians and household members of people with TB, and other community members with no specific experience of TB. Patients, guardians and community members willing to participate were identified with the help of the TB officers at QECH and the MLW community liaison team. None had any experience of the TB-RROC study. Household members were identified by patients and guardians. The FGDs were facilitated by the research assistant (MP). They were conducted in neutral spaces not related to the TB ward at QECH – one in Ndirande Township and the other in Chilomoni Township, both urban areas of Blantyre near to where the majority of study participants reside. Both groups were conducted on a Saturday. Participants were asked to provide informed consent prior to participating. As with the in depth interviews and key informant interviews, FGDs were recorded using a digital

Dictaphone and following the discussion, the research assistant and PI had a debriefing interview from which field notes were made.

7.4.7 Participant feedback

Two participant feedback sessions were organised after key themes had been identified from the data. One session involved patients and guardians in the trial and the other involved healthcare workers. The aim of these sessions was twofold. Firstly, they provided a means of validating the initial analysis of the data; and secondly they were an additional forum for participants to voice opinions and ideas that had not been expressed in their initial interview. The feedback sessions were conducted on hospital premises, but away from the TB ward. The session involving trial participants was conducted by MP in Chichewa, recorded using a digital dictaphone, transcribed and translated into English. The session for healthcare workers was conducted jointly by DC and MP in English and recorded and transcribed directly in English. Due to resource constraints, and the fact that only five participants were from Lilongwe, feedback sessions were only done in Blantyre.

7.4.8 Data collection, management and analysis

All interviews and group discussions were transcribed verbatim in Chichewa and then translated from the Chichewa transcripts directly into English. For quality control purposes, a second transcriber reviewed a random 20% sample of all transcripts. Anonymised transcripts were imported into Nvivo10 QSR software for organising, management and analysis of data. Transcripts were inductively coded and analysed using Thematic Content Analysis. The units of meaning for analysis were text in English (words or phrases), as DC did most coding and is not fluent in Chichewa. All transcripts were read and then re-read before applying free codes to text. Initially, two coders (DC and MP) coded the first 5 transcripts and each independently generated a coding structure, which was shared and discussed in order to produce a unified coding schedule. This coding schedule was used to code further transcripts as the study progressed, and was adapted iteratively as new data was collected. Free nodes within the final coding schedule were collapsed into tree

nodes and used to generate key descriptive themes that summarised the main findings. Data collection was stopped once the key descriptive themes had been identified and no new themes were emerging.

In order to develop more in depth analytical themes, a full day workshop was held which was attended by all collaborators. Workshop participants who had not been involved in the initial coding were familiarised with the raw data by each taking time to read a selection of transcripts. This served two purposes. Firstly, it allowed those members of the study team not directly involved in data collection to become familiar with the data. Secondly, it acted as a check on the initial analysis, particularly as it was recognised that the bulk of the initial coding had been done by DC, who may have brought with her specific biases given her roles in the clinical care of patients and in the TB-RROC trial itself. The initial descriptive themes and coding framework were then presented by DC and MP and agreed upon by the whole group. Following this, more in depth analytical themes and were generated by discussion between the members of the research team. Initially, analytical themes were developed by discussion in pairs. Each pair evaluated two or three of the descriptive themes. Pairs were carefully chosen to ensure a balance between clinicians/non-clinicians and Malawian/Non-Malawian researchers. Following this, discussion between the whole group was used to develop the analytical framework.

7.5 Results

7.5.1 Characteristics of study participants

A summary of the characteristics of study participants and details of in-depth interviews conducted is presented in table 60. In total there were 14 interviews with patients and 12 interviews with guardians who participated in the TB-RROC trial. Of the patients, 6 were in the community group, and of guardians 7 were in the community group. Two participants had experienced readmission after the patient became unwell in the community. Information regarding the 9 key informants is presented in table 61. Key informants were household members of trial participants (2); potential recruits to the trial who declined to participate (3);

nurses (2) and TB Officers (2). Summaries of the observations, feedback sessions and focus group discussions are presented in tables 62, 63 and 64 respectively. All 21 participants from Blantyre who gave an in-depth interview were invited to the first feedback session and 14 were able to attend. The second feedback session was conducted with healthcare workers. In addition to the nurses and TB Officers who were initially interviewed, 2 clinicians from the TB ward at QECH also attended the session.

Table 60. Trial participants and interview details

Participant ID	Role	Age	TB care delivery	Interview Setting	Interview Duration
1	Male patient with male guardian	35	Community	Hospital, BT	54
2	Male guardian of male patient	47	Community	Hospital, BT	60
3	Female guardian of female patient	40	Hospital	Hospital, BT	58
4	Male guardian of male patient	28	Community	Hospital, BT	51
5	Female guardian of male patient	30	Hospital	Hospital, BT	59
6	Male patient with male guardian	35	Community	Hospital, BT	50
7	Male patient with female guardian	36	Hospital	Hospital, BT	74
8	Female guardian of male patient	28	Hospital	Hospital, BT	50
9	Female patient with male guardian	34	Community	Hospital, BT	60
10	Female patient with female guardian	52	Hospital	Hospital, LLW	50
11	Male guardian of male patient	25	Community	Hospital, BT	38
12	Male patient with male guardian	42	Community	Hospital, BT	36
13	Female guardian of female patient	31	Hospital	Hospital, LLW	39
14	Male guardian of female patient	40	Community	Hospital, BT	34
15	Female guardian of female patient	54	Hospital	Home, BT	45
16	Female patient with female guardian	49	Hospital	Home, BT	59
17	Male patient with male guardian	18	Community	Hospital, LLW	34
18	Male guardian of male patient	20	Community	Hospital, LLW	44
19	Male guardian of male patient	21	Community	Hospital, BT	55
20	Male patient with male guardian	32	Community	Home, BT	64
21	Male patient with male guardian	20	Community	Hospital, BT	54
22	Male patient with male guardian	39	Hospital	Hospital, BT	47
23	Male guardian of male patient	21	Hospital	Hospital, BT	54
24	Female patient with no guardian	45	Hospital	Hospital, BT	53
25	Female patient with female guardian	29	Community	Hospital, BT	45
26	Female guardian of female patient	32	Community	Hospital, BT	39

Table 61. Key informants and interview details

Participant ID	Role	Interview Setting	Interview Duration
27	Female household member of trial participants	Hospital, BT	57
28	Male patient who declined to participate in the trial	Hospital, BT	39
29	Female nurse on the TB ward at QECH	Hospital, BT	24
30	Male patient who declined to participate in the trial	Hospital, LLW	30
31	Male TB officer at Blantyre DHO	Hospital, BT	28
32	Male TB officer at QECH	Hospital, BT	28
33	Female guardian who declined to participate in the trial	Hospital, BT	26
34	Female nurse on TB ward at QECH	Hospital, BT	33
35	Female household member of trial participants	Hospital, BT	15

Table 62. Observations

Observation	Brief description	Observation duration
Community 1	Male patient with female guardian visited at home. Guardian observed delivering injection, fieldworker assesses patient & exchanges equipment	60
Community 2	Female patient with female guardian visited at home. Guardian observed delivering injection, fieldworker assesses patient & exchanges equipment	45
Hospital 1	Male TB ward at QECH. Interactions between healthcare workers, guardians and patients observed. Casual conversations with patients on the ward	91
Hospital 2	Female TB ward at QECH. Interactions between healthcare workers, guardians and patients observed. Casual conversations with patients on the ward	60
Hospital 3	Nurses are observed preparing streptomycin for injection the evening before they are they are administered to patients	60
Hospital 4	Nurses are observed (at 5am) administering the pre-prepared syringes of streptomycin to patients on the ward	50

Table 63. Participants in feedback sessions

Participants	Role
Session 1: Trial participants (Duration 75 minutes)	
1	Male patient with male guardian
3	Female guardian of female patient
4	Male guardian of male patient
6	Male patient with male guardian
7	Male patient with female guardian
8	Female guardian of male patient
9	Female patient with male guardian
11	Male guardian of male patient
12	Male patient with male guardian
14	Male guardian of female patient
15	Female guardian of female patient
21	Male patient with male guardian
25	Female patient with female guardian
26	Female guardian of female patient
Session 2: Healthcare workers (Duration 46 minutes)	
31	Male TB officer at Blantyre DHO
32	Male TB officer at QECH
36	Male clinician on TB ward at QECH
37	Female nurse on TB ward at QECH
38	Male clinician at QECH

Table 64. Participants in Focus Group Discussions

Participants	Role	Age	Occupation	Education
Session 1: Ndirande (Duration 90 minutes)				
39	Woman who had had TB	40	Petty trader	Standard 8
40	Woman who had had TB	27	Marketer	College
41	Man who had been a guardian	61	Gardener	Standard 8
42	Man who lived with someone with TB	30	School leaver	Form 4
43	Woman who had been a guardian	35	Housewife	Standard 8
44	Woman who had been a guardian	30	Hawker owner	Form 4
45	Woman community member	23	Petty trader	Standard 7
46	Woman who had been a guardian	36	Hawker owner	Form 2
Session 2: Chilomoni (Duration 72 minutes)				
47	Man who had had TB	34	Minibus driver	Standard 8
48	Woman who had been a guardian	29	Petty trader	College
49	Man who had had TB	39	Gardener	College
50	Man community member	39	HSA	Form 4
51	Woman who had been a guardian	51	Petty trader	None
52	Man who lived with someone with TB	43	Businessman	Form 4
53	Woman who had been a guardian	42	Businesswoman	Standard 8
54	Man who had been a guardian	41	Crane operator	Form 4
55	Woman who had had TB	27	Clothes trader	From 4

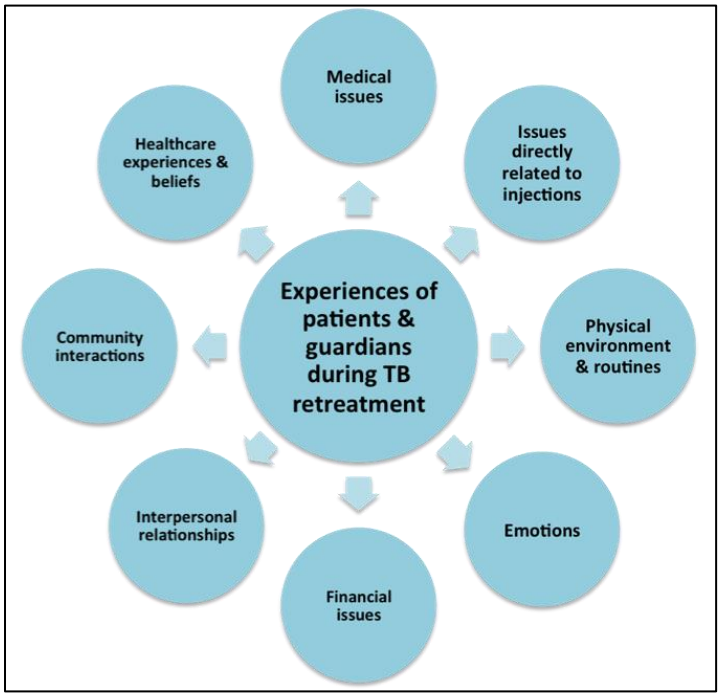
7.5.2 Descriptive themes

This section will present a brief summary of the initial descriptive themes that were developed from the coding framework and used as the basis for discussion during the analytical workshop. Following this, in the next section, the final analytical structure will be presented, in which concepts will be explored and discussed in detail.

From 142 free nodes, 8 tree nodes were generated. These descriptive themes were developed inductively from the original data and are summarised as shown in Figure 37. *Medical issues* included descriptions of the symptoms people experienced; side effects of treatment; the process of accessing medical care and starting treatment; adherence; HIV; acquiring infections from hospital; and health issues for guardians. It was felt that *issues relating directly to injections* required specific attention, as this was the focus of the study. These issues included

complications of injections; the risks posed to others from injections; the process of training to do injections; guardians' ability and willingness to do injections; choosing

Figure 37. Descriptive Themes



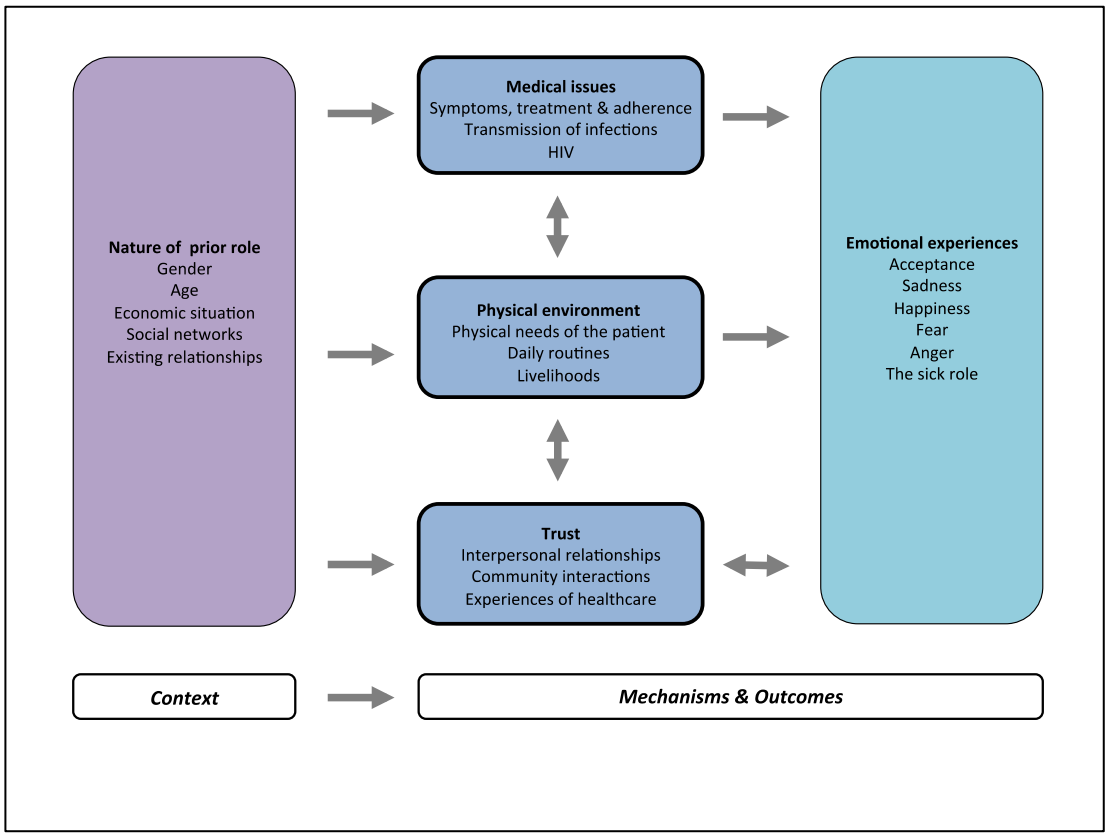
which patients should be injected at home; and the role of lay community injectors. *Physical environments and routines* were a major component of every interview, and common themes that arose were taking care of the physical needs of the patient (including providing food); disruption of daily routines; and the environments of the hospital and home. *Emotional experiences* were varied, both between individuals and within the same interview. They included feelings of sadness, fear, and acceptance. Participant descriptions of the sick role were also included in this theme. *Financial issues* dominated many of the transcripts and had profound effects on people's experience during retreatment. Issues discussed by participants related to the need for more money to cover costs associated with illness; the inability to earn money during treatment; mechanisms employed to overcome the lack of funds; and the effects of financial difficulties, for example being evicted from ones home. Considering the nature of the subject matter, it is perhaps unsurprising that many study participants focussed on their relationships

with others around them. *Interpersonal relationships* discussed included relationships between patients and guardians; relationships between patients, guardians and their families; and relationships between patients and guardians on the ward. Beyond interpersonal relationships, *interactions with the wider community* also influenced experiences. Whilst some encounters with the community were negative, such as stigma and discrimination, it was also evident that the positive experience of support offered by the community played a crucial role. Finally, a key theme was the experience people had of the *healthcare system* itself. Topics discussed included the interactions with healthcare workers; views about the responsibility of the healthcare system; and beliefs about traditional medicine and witchcraft.

7.5.3 Analytical themes

During the analytical workshop, the study team examined these initial descriptive themes further. In depth assessment and examination of the relationships between items resulted in production of the final categories of description and eventual construction of the outcome space. Experiences revolved around three key categories: medical issues, the physical environment, and trust. Each of these experiences were influenced by the nature of participants' prior role (the *context* in which they experienced TB), and in turn resulted in a broad range of emotional experiences. In some instances there were relationships between the central categories (figure 38). Each of the three main categories will now be discussed, referencing interactions between other categories within the network. Themes addressing the first research question ('What are the experiences of patients and guardians on TB retreatment?') are illustrated using quotes within the body of the text. Examples of how the TB-RROC intervention affected these experiences are presented in tables 65 - 67. In line with the overall aims of the evaluation, the tables lay out which mechanisms were triggered by community-based management and how these produced certain outcomes, given the circumstances described by the study participants. Outcomes are focussed on medical, social and economic domains as outlined in chapter 2.

Figure 38. Experiences of patients and guardians during TB retreatment



7.5.3.1 Medical issues

7.5.3.1.1 Symptoms, treatment and adherence

Illness, in particular recurrent TB, is the experience which links every participant in the study. Health problems that patients encountered were therefore at the forefront of their discourse. Participants described the symptoms from which patients suffer in relation to their TB in some detail. Classical symptoms of TB such as cough, shortness of breath, sweating at night and weight loss were frequently reported. Patients and guardians generally demonstrated good understanding and recognition of the symptoms of TB, which was often enhanced by their previous experiences of having had TB:

> *"I had TB treatment for 6 months. When I had it for six months, they said it was enough and that I had been cured. Afterwards, I began to cough again. I began to*

experience shortness of breath whenever I walked, the same experiences I had gone through before. Then I quietly sat down and spoke to myself: 'What is happening to me? Does it mean that the disease is relapsing?"

P24, female patient

Participants' experiences of **accessing healthcare**, going through the process of being diagnosed with TB and starting treatment varied. Delays in accessing care were common, although once again previous experience and quick recognition of TB symptoms often resulted in earlier presentation. In some cases, pre-existing relationships played a part in how patients accessed care. For example, family, community members or even work colleagues encouraged patients to seek medical attention:

"Later on, the person I was working with, the foreman of the place said: 'but we are noticing that your body is kind of losing weight and you are coughing from time to time, you need to go and submit sputum, it could be TB."

P1, Male patient

Table 65. Medical experiences: Symptoms, treatment and adherence

Context	Mechanisms	Outcomes	Illustrative experience	
Treatment				
Guardians have not previously done injections	Guardians trained, feel competent and deliver injections effectively	Clinical outcomes in the community as good as hospital-based care	*"In my case, when I was just starting to undertake that responsibility, I declined. I said I would not manage. But because of encouragement that everyone would manage to train, we really trained and were able to inject on our own."*	P13, Female guardian
Guardians have not previously done injections	Patients trust guardians are trained and allow them to do injections	Clinical outcomes in the community as good as hospital-based care	*"Ah, in my thinking I thought I was going to feel so much pain or the injected area was going to swell if he injected me because he was just learning. But I saw it was just the same as over the two weeks I had been in the hospital and was injected by a doctor. There wasn't any difference."*	P1, Male patient
Guardian's position within family (e.g. young age) means they are told what to do	Guardian 'forced' to take on injecting job, does not feel comfortable in the role, and delivers injections poorly	Clinical outcomes in the community as not good as hospital-based care; Social outcomes poorer from threat to family relationships; feelings of guilt and sadness	*"Ah, it really affected me. Even when I heard that they had taken him back to the hospital, it really affected my life. I felt I was responsible for the problem he had developed. I felt maybe I was the one at fault. I was sad and saying, 'Maybe he is going to hold me responsible for whatever happened.' But then my life rejoiced because … the doctor had told him: 'The problem was not the injector'."*	P19, Male guardian
Patient is in good health	Guardians provide TB medications at home and little additional medical care is required because patient is well	Clinical outcomes in the community as good as hospital-based care; social outcomes better	*"The strategy should be executed depending on the condition of the patient ... people like these critically ill ones require being in the hospital for frequent monitoring by the doctors. But someone who does everything by herself, is strong, hasn't complained about anything, gets out of the bed by herself and manages to move around, could be discharged to go and be injected at home if her guardian manages to inject so that she can perform other household chores."*	P9, Female patient
			"They come only to those who seem healthy. They don't ask someone who is critically sick to be injected at home… that's why they tell you" 'We diagnosed him with TB, he has been admitted for 2 weeks but he looks strong, would you accept to inject him at home?'"	P19, Male guardian

Context	Mechanisms	Outcomes	Illustrative experience	Participant
Transmission of infections				
Overcrowded wards: risk of infection	Fewer hospital acquired infections (for patients & guardians) at home	Clinical outcomes better in the community; lower clinical risk to guardians; less anxiety	*"You would feel sad. It would affect the body… the ward accommodates people with different conditions that you could contract. Therefore you could be affected emotionally."* *"You also think about how critically sick your fiend is, saying 'Eeee! He is not in good shape.' You start pitying yourself … you say 'are we not going to contract diseases from here?'"*	P15, Female guardian P12, Male patient
HIV positive patients in the community	Guardians have needle stick injuries whilst doing injections	Guardians contract HIV infection if not well trained & supported	*"From how they had taught me here, I knew I couldn't contract this disease unless I had pricked myself with the same needle after injecting the patient. But if I injected him and handled the tools carefully and disposed of them I wouldn't contract the virus from him. That's why I completed injecting him without pricking myself or dropping the syringes at any time*	P23, Male guardian
Adherence				
Guardian in a position of less influence than the patient	Guardian unable to insist patient receives injection and therefore adherence poor	Clinical outcomes in the community not as good as hospital-based care	*"… maybe like at home you've been injected by your madam but you've quarrelled on some story so how can that turn out? If your wife is refusing that I won't inject you, what can be the advantage?"* *"I have stayed with him pretty well because he was co-operative in everything I could tell him. I don't know if it's because he was younger and I was older. He may he may have been saying 'he is my senior brother I should listen to him'.''*	P30, Male patient, non participant P2, Male patient
Strong existing relationship between patient & guardian	Guardian able to deliver injections to patient, and gives encouragement to take TB treatment	Clinical outcomes in the community as good as hospital-based care; Social outcomes good as patient - guardian relationships strengthened	*"The most encouragement also comes from you who are staying with him … I would know that maybe he was not going to take the oral medication if I just gave him the injection and departed going into town. I was therefore making sure he took the oral drugs. We just got used to offering one another encouragement and things were progressing without any challenges."*	P4, Male guardian

Additionally, it was recognised that those from poorer backgrounds found it difficult to present to a health facility, often because of lack of money for transport:

> *"Others come from remote areas and fail to go to the hospital because they have no means of transport. When they think about the place being very far away they fail to… get there though they are sick and deteriorating."*
>
> P16, Female patient

Many participants described the **side effects of treatment**. They felt that TB tablets were 'too strong', or 'very powerful' and frequently talked about a relationship between the strength of the tablets and the importance of having food when on treatment. Although these issues applied to TB treatment in general, some participants were aware of, and concerned by, the potential for more serious side effects during retreatment because of the longer duration and the addition of injections compared to their previous treatment:

> *"I started having concern after they had diagnosed me with TB for a second time because in the beginning I had tablets without injection for six months. Two or three years later, I am having the same treatment with additional 60 injections. When I complete these injections I will be on oral treatment for 6 months. So I was very worried right from the first day of the second treatment, wondering if I was not going to develop another problem of high level of drugs in my body."*
>
> *P22, Male patient*

Other treatment related problems specifically concerned the **physical experience of getting injections**, both in hospital and in the community. Apart from feeling pain when the injection was being delivered participants did not frequently describe suffering complications from injections, however the majority were very aware of the potential complications such as swelling or infection at the site of injection, or paralysis of the leg. Most guardians were hesitant to do injections at first because they questioned their own ability and were concerned that they might hurt or cause damage to their patient, but all of them got over these fears once they had been trained to do the injections. Participants recognised the importance of guardians

being trained well before considering community-based management if treatment was to be successful (table 65, P13 & P1).

Although these expressed concerns were extremely common, they were very rarely borne out. In fact, only one patient in the community described having had a complication that required readmission to hospital. The patient was intermittently experiencing swelling at the site of injection and had lost weight. There was no abscess at the site of injections and the patient was admitted for rehydration and treated empirically with antibiotics. As this is an outlying case of participants who had a negative experience, the circumstances of the event do deserve particular attention as they may provide valuable information about the potential for harm. The guardian administering injections was the patient's younger brother. They came from a large family of 8 children. Both brothers described how the younger one was 'forced' to take on injections by the rest of the family. He initially showed reluctance but then accepted and embraced the role. Both described how the guardian drank alcohol, although the guardian said he was never drunk or hung over when doing the injection because of the responsibility he felt towards his brother, whilst the patient recalls a number of instances when he thought his brother was hung-over whilst administering injections. The guardian experienced a range of emotions, including fear, sadness and guilt; and also concern about how this would affect his relationship with his family (table 65, P19).

Most participants describe an improvement in patients' health on TB treatment, with a reduction in symptoms and gradual regaining of strength. '**Becoming strong**' was a well recognised and well received benefit of being on TB treatment, and seen as a key factor when considering whether or not a patient should be cared for at home. Patients, guardians, household members and healthcare workers all recognised that home injections were not appropriate for all patients, and that being well enough was a prerequisite for discharge (table 65, P9 & P19).

Despite seeing improvements in their health, a number of participants referenced TB being a '**deadly**', or dangerous disease. Participants understood TB to be

dangerous for a number of reasons, including delayed presentation and poor adherence. Emotional experiences related to having what was seen as a potentially deadly disease fell into two broad categories. Many expressed fear about what may happen to them or to their patient, and worried about the future, however others accepted the situation and dwelt less on the potential for negative outcome:

> *"I will take TB treatment that is provided by the hospital and see how far it is going to get me. If it's time to die, I'm going to die. If the time is not yet, you can't die."*
>
> P24, Female patient

Some participants gave examples of how they had not adhered to TB treatment in the past, but none admitted **non-adherence** during the current episode. There was a good understanding of the consequences of non-adherence, with some going as far as explaining the concept of drug resistance:

> *"If you stopped treatment and wanted to start again, the bacteria will have developed resistance. Even when the hospital gives you treatment, it doesn't help and you just die eventually."*
>
> P24, Female patient

Participants perceived adherence, or lack of, as being related to treatment factors (such as length of treatment and side effects); health factors (such as feeling better and no longer seeing the need to take treatment); and personal factors, which were often affected by a patient's pre-existing situation. For example, it was perceived that people commonly failed to adhere to treatment because of interactions within their social networks that involved alcohol (even when still admitted to hospital), but here gender did play a role, as alcohol was only discussed in reference to men:

> *"….there were a couple of people who I saw in the hospital. While they were getting injections, they were also going out to drink and return to the ward. Some of them even ran away from hospital without completing medication."*
>
> *P20, Male patient*

There were concerns expressed about the *potential* for non-adherence to injections for those managed at home, often by those who had not participated in the trial. A common reason offered for why doses might be missed in the community related to the interpersonal relationships between the patient, guardian and family. More specifically, it was perceived that guardians in certain positions – such as wives, or younger siblings – would be unable to insist on giving an injection to a patient who was refusing; or that arguments within families would mean that guardians could refuse to care for the patient properly (table 65, P30 & P2). However, these remained perceived problems. They were not realised in any of the accounts given by those in the community arm of the study, and none of the participants described a single missed injection. The closest situation in which an injection may have been missed was when a guardian (uncle to the patient) argued with his sister (mother of the patient) about an unrelated episode. He then threatened to walk away from the task of injecting, but after discussion did not follow through and gave all the doses according to schedule. This is an example of the potential for the injector role to be used as a control mechanism within a family, but it was related more to the existing relationships within the family than to caring for the patient, and did not result in actual harm. In fact, more often guardians played a positive role in supporting patients to adhere to treatment, with most reports recognising the importance of guardians (table 65, P4).

7.5.3.1.2 HIV

Most patients were HIV positive so that HIV infection as well as TB was an important component of peoples' medical experiences. The majority of patients had already received their HIV diagnosis and were on ART prior to their current TB episode. In cases where the patient or guardian was finding out their status for the first time or the patient was failing ART, medical aspects of HIV featured more strongly. The **interactions between TB and HIV** in terms of increased risk of TB in HIV, reduced immunity and effects of drugs were well recognised.

"If you contract HIV then TB follows you too. It's right behind you."

P10, Female patient

"I feel that the main factor was decreased immunity in her body because her body did not accept the ARVs and they have now given her second line ARVs. The immunity was very low in her body and because of reduced immunity TB found the opportunity to relapse."

P15, Female guardian

Issues around disclosure of TB-HIV status were related to interpersonal relationships and interactions with the community (see section 7.5.3.3.).

7.5.3.1.3 Transmission of infections

Concerns about contracting infections were common. These included getting TB from the patient, getting TB from the hospital, getting other infections from hospital, and risks of HIV transmission from injections. In this way 'medical issues' are closely related to the 'physical environment,' and reducing the risk of contracting infections from hospital was seen as a major advantage of community-based care (table 65, P15). Concerns about transmission of infection sometimes affected personal and community relationships (see section 7.5.3.3.). Emotional responses to the risk of infection were usually negative ('fear' and 'sadness') but trial participants had to deal with their concerns and always ended up accepting the risks. Participants were concerned about guardians acquiring TB:

"The guardians are at risk of this same TB. I have seen a couple of women who came back to the hospital infected with TB two or three months after being guardians for their husbands."

P34, Female nurse

And also the risks of getting infections other than TB from the hospital:

> *"I also felt at risk of other infections and was worried … You would have a critically ill patient struggling to get to the toilet and soiling himself on the bed just next to you. I felt I was in danger of other infections than the one I was in the hospital for. That's what I was very much worried about. I feared I might develop another condition if I got well from the disease I already had."*
>
> *P22, Male patient*

Some guardians expressed initial concerns about the risks of acquiring HIV from needle stick injury whilst doing injections, but they were more confident having received training (table 65, P23). Others were worried about having needles at home if there were children in the house, although by safely storing equipment, once again they all managed to find ways to avert the fears they had at the beginning. None of the participants reported a needle stick injury. Although it is possible that trial participants might not have reported needlestick injuries for fear of being seen to have failed, they were given opportunity to discuss this during interviews and none reported a needlestick injury.

7.5.3.2 The physical environment

7.5.3.2.1 The physical needs of the patient

Attending to the physical needs of the patient formed a major component of the experiences of all those involved in caring for people with TB. Making sure that patients are able to wash, go to the toilet and have a clean, warm bed were key activities. **Food** has already featured heavily - as a side effect of treatment (reduced appetite, weight loss) and as being important for the recovery of the patient. Providing food was a central theme and consumed much time, money and energy. It is of interest that experiences of food depended very much on the hospital context - food on the ward in Blantyre was not thought to be adequate, and people felt the need to bring food for the patient and guardian from home, but in Lilongwe

food provided by the hospital was thought to be of high standard, and in some circumstances was even a reason for not wanting to be discharged.

In the ward, one main guardian usually carried out the task of caring for a patient, but **responsibility was often shared** amongst family members and the community, and frequently depended on the availability of funds. Similarly, for those managed at home, these tasks tended to be done primarily by one main carer with the support of others at times, but more frequently the patient was able to take responsibility for their own care. Whether activities of daily living were an individual or collective responsibility was determined in large part by prior circumstances, such as existing economic situation, social support and existing relationships. Likewise current relationships with the community, healthcare workers and even other patients and guardians on the ward also affected the ability to deal with daily physical needs (see section 7.5.3.2.). The importance of having good pre-existing relationships is demonstrated by discussion about those patients who did not have a guardian:

> *"Challenges of being in a hospital appear if you the patient are not strong to get up from where you are sleeping because it becomes really hard if you depend on yourself for everything. How are you going to collect your porridge? How are you going to feed yourself if you have no guardian? Who is going to persuade you to take the medication because you need a guardian to collect the drugs and help you take them. This is a very big problem."*
>
> *P24, Female patient with no guardian*

In contrast, those with strong **social networks** found support from their families and communities who provided assistance, for example bringing food. One of the main advantages of community-based care was relieving the burden of others having to come to the hospital to provide food (table 66, P12).

Table 66. The physical environment

Context	Mechanisms	Outcomes	Illustrative experience	Participant
Providing for the physical needs of the patient				
Those in hospital rely heavily on community	Easier for people to visit and support patients at home as it is quicker and less expensive	Strong community relationships are maintained; burden on community relieved	*"It's a very helpful program because you also relieve other people. There are other disadvantaged people who can't manage to travel from their homes daily coming to see you with food, or other people who want to come and see you every day."*	P12, Male patient
Poor hospital catering (Blantyre v Lilongwe)	People have to bring food to hospital (burden on community)	Bad hospital food is an incentive to go home, good food incentive to stay	*Food is available at the hospital, but it is not of good quality…the porridge that is offered in the morning is purely watery, it is not even porridge… a patient could not take that porridge only until lunch time. The 'ndiwo*' is not good for someone to eat… of course, someone could take it but they wouldn't get the necessary vitamins or nutrients."*	P15, Female guardian
Daily routines				
Daily routines interrupted by hospital admission	Patients and guardians at home are able to continue daily routines	Patients and guardians able to maintain dignity and independence	*"My life was not affected because the job [injecting the patient] did not last many minutes. You perform it once right there and then you start carrying out other tasks. So there wasn't any problem. It did not disturb me. It's just the same."*	P11, Male guardian
Relationships disrupted by hospital admission	Patients and guardians at home are able to continue social interactions	Patients & guardians better able to maintain community relationships	*"I felt good about getting injected at home for you never feel anxious about how you are going to see your friends."*	P17, Male patient
Daily routines interrupted by hospital admission	Patients and guardians at home are able to go to school and church	Children are able to go to school (and church); relationships are maintained	*"… there is also time to go and worship … I would not have been able to write standard 8 examinations if I stayed at hospital here … the reason he [my guardian] accepted to inject me was because he too is in school*	P17, Male patient
Daily routines interrupted by hospital admission	Patients at home feel more 'normal,' and therefore less 'like a patient' (sick role)	Dignity and independence maintained	*"When you are taking medication at home it feels like you are not on medication. It feels like you are just staying. When someone sees you they say 'Ah, he is not sick,' when you are actually sick, because you are able to perform household work on your own. When you are in the hospital … all you think about its 'I am in the hospital' and the sickness worsens."*	P12, Male patient

**Ndiwo = relish*

Context	Mechanisms	Outcomes	Illustrative experience	Participant
Livelihoods				
People have to run two households when patient in hospital	Food is shared and there are no transport costs when patients are at home	Reduced costs to patients and households	*"If someone has been admitted to hospital transport costs can make them poor because it means they have two households: they should take care of home and come here to see the patient … at home they should fetch for food and also at the hospital, and also money for transport."*	P29, Female nurse
Inability to work when in hospital	Patients and guardians at home are able to work	Reduced lost earnings for patients and households	*"The problems I went through … because each time we came to the hospital here, the business also stopped"*	P4, Male guardian

7.5.3.2.2 Daily routines

Trial participants found the **ward environment** distressing, and described in detail the unpleasant reality of daily life in hospital. The predominant feature for all participants was overcrowding, which affected people on many levels – the physical discomfort of not having enough space, the lack of privacy and dignity, the risk of infection, difficulty in getting care, and the anxiety associated with being in close proximity to seriously unwell people:

> *"The disadvantage is where we stay. We stay in a place where we are squeezed in where people sleep, beds touch each other unaware of what the other is suffering from. That is what makes the hospital to become a problem."*
>
> P 28, Male patient who declined to participate in the trial

> *"Now the ward is always full meaning that patients are sleeping on the floor maybe even failing to pass because it is full ... it becomes difficult for you to take care of someone who is under the bed."*
>
> P29, Female nurse

Overcrowding was also related to a lack of hygiene on the ward, which was often a painful experience:

> *"You find that they fail to mop because someone is sleeping on the floor. They fail to use disinfectants. In the end they just mop the corridors forgetting that they are supposed to mop under the bed."*
>
> P31, Male TB officer

> *"This time their nostrils have detected a bad smell. As they enquire from one another where the smell is coming from, they discover it is from the patient just next to them, the one with a small baby. She has been soiling herself up since morning and can't bathe because there is no water.*
> *'The smell is too bad,' one of them complains.*

The woman doesn't respond. She quietly walks to the sink just close to where I am to see if there is water, but still there is no water.
'So what do you do when it is like this?' I ask her
'Nothing, we just wait until the water comes back,' she replies''

Hospital observation 2

Guardians frequently expressed their unhappiness about not being allowed **access to the ward**, particularly in the morning when doctors did rounds or the ward was being cleaned. They felt that their patients might be neglected; that their time was being wasted being 'idle' outside the ward; and that they should be available during consultations with healthcare workers to provide and obtain information about the condition of their patient.

"Life in hospital is challenging. The time I was in hospital, being a guardian, they had to wake me up at 5 am saying 'wake up! Go outside, we want to clean the room! That means the patient had to stay alone. We had to stay outside until they had completed their work …. If the patient wanted something, there was no way she could communicate to you."

P26, Female guardian

The **ward environment at night** was a particular discomfort for many. Guardians usually slept on the floor under the bed of their patient. This was particularly bad for women who often slept in the same ward with men, which many found extremely uncomfortable. However, in contrast to a situation outside the hospital, this was acceptable, because they were there to look after a patient.

"Where to sleep was so much of a problem because we used to spread chitenje on the cement floor and sleep there till morning, at times not even sleeping at all."

P5 Female guardian

Admission to hospital caused massive, often disastrous, disruption to peoples' usual daily routines. In addition to escaping the distressing living conditions on the ward, being able to **continue normal activities** such as going to school and church was a

major advantage for those managed at home (table 66, P11 & p17). Many trial participants described the phenomenon that 'things just stopped' during their time in hospital. Taking on the responsibility of caring for patients resulted in people 'being busy', which was seen as a bad thing because it interrupted the pattern of peoples' lives. Having a patient was especially bad if it caused many people to 'be busy.' The effects on daily routines depended on the circumstances of the patient or guardian, and was more significant for those who previously had provider or carer roles within the household. It was not clear that gender played a role in this effect per se, as it was not only men who had provider roles and many women worked too:

> *"My family is also one of the areas that got affected. I was the one responsible for running the affairs of the household, and I was also the same person who got sick. Therefore everything seemed to stop."*
>
> P10, Female patient

Many people attempted to continue normal routines whilst on the ward – guardians dividing their time between caring for the patient and maintaining their usual activities, and even patients themselves, who were often well enough, leaving the ward to visit family or to go to work.

A consequence of being able to function more 'normally' at home was often a change in the emotional state of the patient. Many describe feeling less like a patient once they went home, and this was seen to aid their recovery, and changed their 'sick role' in the community (table 66, P12).

7.5.3.2.3 Livelihoods

Illness and admission to hospital often had catastrophic effects on peoples' income and financial stability, and frequently left them extremely economically vulnerable. The increased costs to households were primarily **costs of food and transport**,

which were a major feature of being in hospital. Costs were reduced for people at home as they no longer had to run two households (table 66, P29).

The greater financial need during sickness was compounded in many cases by **not being able to work**, which again affected both guardians and patients. This was frequently dependent on their prior economic situation. Those who had fixed employment had variable experiences during their admission – many were not paid, some lost their jobs entirely, and others managed to continue going to work. Those running small informal enterprises sometimes lost their livelihood, but for others the increased flexibility meant that they were able to make arrangements to continue the business and often rearranged their schedules to fit around caring for the patient. This was also dependent on social networks, which, if strong, could be called upon to assist, but if weak meant no help:

> *"On the side of the business, the time I was in hospital I had kept 25,000 kwacha at home. Since my senior sister also likes doing the business of trading textiles, I said to her …. 'use the money for ordering chitenje. She used the money and sold them on credit. When I got out of here, I resumed the business.'"*
>
> P13, Female guardian

Coping mechanisms for financial difficulties most often involved borrowing money, but trial participants also described having to sell items that they owned. Participants in both arms of the trial describe having to borrow money, but it was always related to the costs associated with hospital admission. Men and women both took loans, but, except for two students who had help from relatives, they were all people who had either employment or an existing small business. Yet again, patients and guardians relied heavily on their existing social support systems, rather than taking formal loans. People borrowed from relatives, friends, from their own businesses and in one case from a 'community bank' established in her village; and often struggled to repay the loans. The experience of having to employ financial coping mechanisms did not seem to be affected by gender or age. Both men and women, young and old borrowed frequently and there were no clear patterns

which differentiated different groups in terms of financial coping. The consequences of financial difficulties were sometimes devastating. Needless to say, where economic problems did arise they resulted in deep emotional experiences, causing fear and anxiety, irrespective of personal and social circumstances:

> *"I was full of worries, saying to myself, 'I obtained a loan just recently and they are saying I should be admitted.' My life was sad all the time thinking about the loan and the sickness."*
>
> P24, Female patient

7.5.3.3 Trust

Issues around trust affected interpersonal relationships, relationships with the broader community and interactions with the health care system. These interactions lead to a range of emotions, such as sadness about leaving children at home, and anger at certain aspects of the healthcare system. In turn, this could affect peoples' faith in those people and institutions around them.

7.5.3.3.1 Interpersonal relationships

In general, relationships between patients and guardians were strong and very positive in both the hospital and community groups. Most describe the love between them, with the guardian caring for the patient 'wholeheartedly'. The job of the guardian was broad and multifaceted. It included practical activities such as washing, bathing and feeding; helping with medical care for example giving tablets (or injections), and monitoring the patients' condition; as well as providing emotional support and companionship. Such close interactions often strengthened the relationship between the two, particularly if the guardian was injecting (table 67, P23).

Guardians showed enormous **commitment**, frequently demonstrating huge sacrifice in order to put the needs of their patients first. Particularly when patients

were in hospital, not only did guardians give up their time, they often also sacrificed money, work, school, their own security and dignity, and relationships with their families. In one extreme example, a young woman left four small children at home alone, lost her job, and was evicted from her house in order to care for her sick brother. Although this was a huge burden, she did not resent her brother in anyway. This was another area where 'acceptance' featured strongly, with people giving up a lot in order to look after their patient:

> *"The 60 days hurt her more than me because it reached a point of her lying to me that she had eaten already just to ensure that I ate the little food that became available when actually she had not eaten. She would stay without eating."*
>
> P7, Male patient

Much of this closeness derived from deep **trust** in one another. The patient was required to trust the guardian to care for them; and the guardian needed to trust that the patient would allow them to carry out their duties. This was especially important for those managed in the community. A suggestion from some participants in the community arm was for patients to be present when guardians were being trained to do injections, so that they would both be able to take on the responsibility of doing the injections correctly and their trust in each other would be even greater (table 67, P2).

The respect and faith patients and guardians had in one another depended in part on the **motivations people had for taking on the role of carer**, and the process by which a guardian was chosen. There were both internal factors (the guardians' own sense of duty), and external factors which affected peoples' decision to become a guardian. Many felt an intrinsic sense of duty to care for a patient who was unwell. They volunteered themselves willingly because they loved their patient and because they simply wanted to see them get well. Commonly, people did not even question whether or not to be a guardian – the motivation for accepting the role was simply that the patient was sick and needed caring for; no other explanation was necessary. Factors external to people's own sense of duty also affected who

became a guardian and included family pressure, a fear of being shunned by the community, and being instructed by healthcare workers. Some guardians were nominated by others, either family members or the patient themselves. It was recognised that the existing relationship between patient and guardian was crucial to how they would interact during treatment, and therefore how well the treatment would go, especially in situations where the guardian had taken on the responsibility of injecting (table 67 P14 & P34).

Table 67. Trust

Context	Mechanisms	Outcomes	Illustrative experience	Participant
Interpersonal relationships				
Patients and guardians have good relationship	Patients and guardians learn to depend more on each other, and develop deep trust	Improved relationships between patient and guardian	*"It denotes love, the love that you have for that person, because it's hard to help somebody you don't love. But if you love that person and help him wholeheartedly, I think your relationship with that person improves. And that person accepts you because he knows you are going to help him."*	P23, male guardian
Patients present during training about giving injections	Patients understand how to give injections, they check guardian technique, ensuring safe delivery & enhancing confidence	Improved relationships between patient and guardian; Good clinical outcome	*"It could also be a good idea for doctors to ensure that when they are training this person to administer the treatment, the patient should be there too … so that when they go home, when one stops the other from doing something prohibited, the other shouldn't disagree."*	P2, male guardian
Patients and guardians have bad relationship	Extra burden of caring for the patient puts strain on the relationship	Worsening of relationship between patient and guardian	*"The guardian needs to be someone who already relates well with the patient. You can't take someone who doesn't get along with the patient to be guardian. Then there is going to be some ill treatment between them … that is why the patient is given the opportunity to pick someone who should be caring for her."* *"Others decline to be guardians because of lack of love for their patient. If they had disputes in their family or did not get along with her before, many find it hard to come and help her."*	P14, male guardian P34, female nurse
Families have children at home	Patients and guardians able to look after children at home; reduced anxiety about neglecting children	Children receive better support and care; emotional distress of parents is reduced	*"I had a small kid … the time I was in the hospital the kid looked like a child with no parents. She would go and wait for food in people's homes. She would move around uncontrollably … it would bother me greatly in my life."*	P16, female patient
Community interactions				
Heavy reliance by patients & guardians on community	Patients and guardians able to take care of their own households when at home	Children receive better support; patient and guardian have better position in community; independence maintained	*"Children were being taken care of. Other people could support them for us: 'oh, children what do you have in the house?' 'Ah, there is nothing.' Then whoever had something would take the little they had and offer it to the children because they were all young."*	P10, female patient

High level of TB-HIV awareness	Community based care avoids disclosure of TB (and HIV) status	Dignity and independence maintained as patient confidentiality protected	*"if you have been admitted to hospital for 2 months people know that you are also HIV positive"*	P10, female patient
Guardian has good social network	Community willing to accept new role, and recognises the benefits of guardians injecting	Guardian gains respected position in the community	*"If I told them they would praise me saying 'you did a great thing accepting to inject him because others would have remained in the hospital being afraid of learning to give injection,' so many would encourage me."*	P18, male guardian
Experiences of healthcare system				
Under-resourced health system & poor families	Patients unable to access healthcare if they deteriorate at home due to lack of ambulances, phones, transport	Poor clinical outcomes in the community; potential for anxiety about what would happen if patient deteriorates at home (helped by understanding process to access care)	*"Admission to the hospital is good because at the hospital is where they know more. If you complain of something and they carry out an examination on you, they are able to determine the disease you are suffering from, but at home we wouldn't be able to tell."* *"When I was re-admitted to the hospital, the nurse asked me 'are you going back home again?' I told her 'no, I should complete the treatment here.' I thought it was good to complete the treatment here because I could speak to a nurse if I felt something in my body."*	P10, Female patient P20, Male patient
Traditional model of healthcare, users are passive	Patients and guardians feel empowered as they share responsibility of healthcare by doing injections at home	Increased engagement with health care	*"They say doing injections is for healthcare workers, but when doing this work it is like we are saying that this problem is for everyone and everyone at home will receive it with both hands."* *"This program could have good outcomes because through receiving the training we have known how TB works, what it does and what we need to do. This can spread the message so that it reaches other people.'*	P29, Female nurse P5, female guardian
Sick people in community unable or unwilling to access care	Guardians trained become 'lay injectors' in the community and deliver injections without supervision	Unsafe injections by lay injectors in the community lead to medical complications	*"No. I was only trained to inject the patient from whom I was a guardian. You are responsible only for your patient... Unless healthcare workers themselves instruct you to go somewhere and inject somebody … you can't do that on your own. It would be an offense for you are not sure about the medications required for that person … You could even have somebody suffering from the same disease as your patient, but I learnt that if you are to inject somebody, you need to know how much they are weighing and their weight determines their dosage."*	P23, male guardian
Under-resourced health system	Guardians trained to give injections take on supervised volunteer role in the community	Safely delivered injections in the community relieves burden on health system & users; Guardians sense of achievement in sharing responsibility for care	*"I think I have found a certain life fulfilment that people have. And I have been fighting hard, that if possible, if God pleases, I should join this medical field and be one of the people doing this work because this work is good. Whenever I was helping the patient I felt I was doing something great … if they ask me to go and inject somewhere, I can do that provided they tell me how to prepare the medicine."*	P23, Male guardian

It was often the case that a family decided together which one of them should take primary responsibility. There were some guardians who declined to participate in the study because of fear that if something went wrong during the course of injections they would be blamed by the rest of the family. As previously seen (section 7.5.3.1), sometimes younger family members were instructed to be the guardian based on a decision made by the rest of the family. Whilst age played some role in choice of guardian, the data do not suggest that gender did. Although being a guardian is often associated with a caring role traditionally taken on by women, men and women both took on the role frequently and just as willingly. Not only performing injections (which may have been seen as having higher status), but taking care of the daily needs of the patient seemed to be entirely compatible with masculinity. Many of these issues around deciding who should be a guardian were similar when choosing who should care for a patient in hospital, and who should take on the role of injecting. One difference was that older women sometimes felt less confident to learn how to inject.

Finally, some people were motivated to take on the role of guardian in the hope that it would be reciprocated if they got sick at some time in the future:

> *"The love you have for that person is what motivates you to be a guardian, because everyone falls sick. Today it's him, tomorrow it's you. If you become sick yourself, the person you helped will say 'this person helped me so I should help him too,' because sickness knows no age or status."*
>
> P19, Male guardian

In general, **relationships within families** were maintained. The family usually pulled together to support both guardian and patient in hospital. However, family dynamics often suffered, primarily because those in hospital felt that they were neglecting their children during the long admission. Sadness and worries about children who were left unsupported at home were common. This became part of the difficulty of being in hospital, and was one of the major attractions of community-based management (table 67, P16).

Effects on interpersonal relationships were not limited to families. In many instances strong **relationships developed between those living on the ward**, where a short-term community of patients and guardians was seen to develop. Patients looked out for each other, sometimes filling the gap for those without strong existing social support mechanisms by caring for those patients without guardians. Guardians likewise shared the burden of responsibility by seeing to each other's patients if one had to be away from the ward.

> *"He did not have a guardian, and once I bathed him. And the example I demonstrated influenced all the other people around to follow suit. When it was morning, one would go and warm some water for him … we kept doing that until things started improving for him."*
>
> P7, Male patient

The members of the ward community described comfort from the discussions they had amongst themselves about medical problems, medications, families, food, healthcare workers, and even about this study. Food was shared between those on the ward, and some guardians described praying together or having informal church services in the shelters. Furthermore, the accounts of friendships that developed on the ward were some of the times when happiness and even having fun were most evident:

> *"There is a video song playing on the television and the thin patient starts dancing to it. She dances whilst sitting on her bed and others in the room laugh with her."*
>
> Hospital observation 2

Although no participants in the community described a feeling of missing out on being part of the 'ward community,' nevertheless, this support structure may have offered the benefits of camaraderie and shared experience which patients at home would not benefit from.

7.5.3.3.2 Community interactions

The vast majority of **interactions within society were overwhelmingly positive**, with those affected by illness relying heavily on the support of their communities. Occasionally, patients and guardians felt themselves to be a burden, but almost always they gained comfort from the people around them. Community members were trusted to support children left alone at home, visit those in hospital, and even provide financial help. These responsibilities were greatest when patients were admitted to hospital and relieved for patients managed at home (table 67, P10). Frequently, the onus was shared amongst many in the community who often took on many of the same responsibilities as family members.

> *"Many people knew of my problem and it pleased them to offer me a hand. My friends, neighbours and some of my relatives were the ones who played the role of helping me, paying house rentals for me, even looking after my children. It was a challenge for me and I don't know how it would have been dealt with if it were not for these people."*
>
> P7, Male patient

Yet again, peoples' previous roles within their communities often influenced the support they received. Some community support came from friends and neighbours, but for those who had weaker **social networks** on which they could not rely, more formal networks were sometimes able to step in. For example, many got help from the religious groups to which they belonged, or even from communities established within a work environment:

> *"My job stopped the moment I got sick. But with the committee we formed, we don't forget one another. If a member has been admitted to a hospital maybe for 2 or 3 weeks, drivers as well as conductors go there to see him … they formed this committee because previously if one of us minibus drivers got admitted, he would stay in hospital without being visited until he passed on or was discharged."*
>
> P20, Male patient

Despite the heavy reliance on community members during illness, issues around disclosure of health status and **stigma** still featured. In general, people felt more comfortable disclosing their TB diagnosis than their HIV diagnosis, but there was recognition of the link between HIV and TB. It was often felt that admission to the medical ward was in effect a disclosure of HIV status. In one case a participant claimed that "if you have been admitted to hospital for two months people know that you are also HIV positive," demonstrating his perception that the significance of a two-month admission for retreatment TB was well recognised in the community as being associated with HIV. By shortening admission time to the TB ward to less than two months, the problem of disclosure by this mechanism can potentially be avoided. Not all participants expressed concerns about discrimination in the community, and for those who did it was almost always related to people's fear of contracting TB.

Most participants at home did not **disclose** beyond the household that the guardian was administering injections. However there were concerns, mainly from health care workers and attendees at FGDs rather than study participants, that injecting at home would cause problems in the community. They feared that even if patients did not tell people they were being injected at home, gossip in the neighbourhood would lead to people finding out and stigmatising patients because they associate injections with severe forms of TB. Once again, this abstract experience was not borne out in concrete experience - none of the concerns about gossip were realised by any of those who received community based care. In reality, when participants informed others about home injecting, guardians seemed to get great respect from the community for the helping role they were playing (table 67, P18).

7.5.3.3.3 Experiences of the Healthcare System

Trial participants described mixed experiences of their interactions with healthcare workers. A small number complained of negative interactions with nurses, including feeling that their patients were being neglected (e.g. delays in changing a drip); and

being shouted at for complaining or asking for help. However, it was well recognised by patients and guardians as well as the healthcare workers that the overcrowded environment on the ward made the job delivering care harder, and affected the ability of nurses in particular to look after patients well.

Views about where the **responsibility lies for the care** of the sick varied. Although it was seen that responsibility for diagnosis and prescription of treatment lay clearly with the healthcare system, care for patients after this point was seen mostly as a shared responsibility. This was the view of both trial participants and healthcare workers; in fact there was a clear understanding from all perspectives about the division of labour and the responsibilities of the guardian. Guardians took on the majority of the care in terms of hygiene and nutrition, but some participants also felt this should be the responsibility of the health care system, especially when patients do not have a guardian. Conversely, most people felt that the health system should be primarily responsible for the health needs of patients, but that guardians, family members and even patients themselves also shared this responsibility. For example patients, guardians and nurses described the clear role that guardians played in monitoring the condition of the patient and reporting to the nurses if a patient became unwell, as well as encouraging patients to take medication. In this example, patients are expected to take on the responsibility of registering themselves for TB treatment and submitting sputum, rather than the healthcare worker knowing who on the ward needed to be registered, a situation which may well have resulted in patients not registering if they were too unwell or not in the ward at the time:

> *"A male TB officer enters the room. He is looking for patients who have been on the ward since a week ago. Four patients raise their hands. He sees them one by one. He gives to each one two small glass bottles. He first labels the bottles and then says, 'these bottles are for sputum collection."*
>
> Hospital observation 1

Specifically relating to community-based management of injections, people believed it was the responsibility of doctors and nurses, but most recognised that guardians could take on the job if they were properly trained, because they saw the advantages of home-based care. However there were concerns about what would happen if a patient became unwell whilst at home. It was clearly felt that one advantage of hospital-based over community-based management was being close to doctors and nurses and being able to **access help** quickly if the patient's condition deteriorated (table 67, P10 & P20). This is made worse by the fact that the circumstances in Malawi mean there is little access to emergency services such as ambulances, and patients with little income have to finance their own transport and communication with healthcare facilities. However, once again this theoretical concern was not realised in any actual experience, as no participants describe a situation in which they were, or even felt as if they were, stuck in the community with no access to care.

There were no instances where guardians administered injections to people other than the patient they were trained to inject, and all said that they would not consider doing so without instruction from the hospital. Not only did all guardians deny **injecting members of their communities**, they were able to give very clear reasons why they would never do so (table 67, P23). However, in one community observation the guardian enrolled into the trial was a nurse and had taught the patient's wife how to administer the injections. This was picked up by the trial fieldworker during the visit, and was the only example of such an incident throughout the trial. The wife was then formally trained by the study team, officially became the patient's guardian and successfully completed injections. Most guardians were proud of their accomplishments and were keen to offer their help in future if it were needed, and properly supervised.

Only one participant, who declined to participate in the trial, expressed concern that if she took a patient home for injections, she might be **bewitched** "so that they can claim if he is sick it is because of this research idea of discharging somebody to receive injections at home," (P33) but this seemed related more to research per se

than injecting in the community. There were very few other references to traditional medicine or witchcraft, other than the acknowledgement that delays in accessing hospital care caused by first going to traditional healers may worsen a patient's condition.

Overall, feelings about community-based management of patients receiving injections as part of TB treatment were extremely positive. The advantages in terms of medical care, daily routines, financial stability, family relationships (especially with children), and burden on the community were overwhelming. However, it was recognised that successful home-based care depended very strongly on two factors: firstly, **adequate training** of guardians and support from the hospital when needed; and secondly that only **patients who are well enough** to be at home are selected.

> *"They discharged us such that we got relieved of other things after we had gone home. We were now spending less money than when we used to come here because transport and food costs used to be high. For some of the relatives who were unable to come and see him because of lack of transport, it became lighter. Many people have been coming to the house to see him. The patient too transformed in his life because he was able to differentiate being at home from being here. At home, he had the sensation of being healed because he was able to meet with everyone."*
>
> P4, Male guardian

7.6 Discussion

Evaluation of the lived experiences of patients and their guardians during the intensive phase of TB retreatment produced three main categories of description: medical issues, the physical environment and trust. Experiences were often influenced by context of the patients' and guardians' prior roles within their communities and households, and resulted in a range of emotional responses. Community-based management affected experiences in all three categories of

description, and again these experiences were impacted on by previous roles and backgrounds.

The data have important implications for the interpretation of the TB-RROC trial, and add to the overall evaluation of the intervention. The categories of description that have been identified, and the interactions between them, highlight some of the advantages and disadvantages of community versus hospital-based care during TB retreatment in terms of medical, financial, social and emotional outcomes. Additionally, the data provide information which helps to address some of the concerns initially raised by stakeholders such as the community advisory board, medical ethics boards, and the National TB Control Programme. Finally, they provide useful insights into ways in which the intervention could be improved to maximise benefit and improve experiences.

7.6.1 Financial consequences

A striking finding is the disastrous effect that admission to hospital has on peoples' ability to continue normal daily life, and in particular the catastrophic consequences of this on their livelihoods. Once discharged, those in the community were relieved of many of their expenses and more easily able to return to their usual routines, thus relieving some of the economic pressures and associated emotional stress. However, it is important to acknowledge that financial burden was felt by those in both arms of the study with higher costs and reduced ability to earn money being primarily, but not exclusively, limited to the period of hospitalisation.

It is of note that the economic burden of hospital admission and the financial advantage offered by community-based care did not appear to be particularly affected by age or gender. The economic vulnerability of women has often been reported, but the data in this study are reproduced in the qualitative and economic evaluations which both demonstrate that the intervention was cost saving for households, irrespective of the gender of the patient. This difference may be explained by the fact that most trial participants did have some income, even if it

was not in the form of a regular salary therefore they still felt the financial effects of illness, and by the fact that the evaluation focussed on effects on the household, not simply on the individual recruited.

7.6.2 Social experience

Socially, the advantages of a community-based model were also evident. Patients, guardians, family members and the wider community were all affected by the necessity for care to be provided for those in hospital. Social capital is widely recognised to be a crucial component of peoples' ability to access care, engage with health systems and remain in treatment [481-483]. Although solidarity from social networks or 'the clanship system' [466] have traditionally been seen as fundamental to the structure of many African societies, it has also been reported that the main source of assistance (and therefore duty) lies within the household rather than with the wider community. For example, in an ethnographic study in the Ivory Coast, Bossart reports that household members play a key role in the management of illness, but that their help is often taken for granted, considered an obligation and based on traditional gender roles [484]. In the context of strong social networks, those admitted to hospital in this study were able to rely on both families and broader social groups to help with the practicalities of being sick, whereas those with weaker social networks suffered. In contrast to previous studies [485-487], the role of guardian was not particularly gendered with men and women taking equal responsibility for all aspects of care. It is unclear why this intervention did seem to override gendered household norms. It may have been that the task of administering injections was seen as more important (and therefore more appropriate for men to take on) than other traditional roles played by guardians such as washing and cleaning. However, approximately one third of guardians in each group were male, and the interviews demonstrate that, by and large, male guardians enrolled into the trial continued in their guardian roles even after being randomised to hospital-based care. Once again, the burdens of care on family and social support structures were relieved to a large extent, but not entirely, by being in the community.

The commitment and sacrifice shown by carers was often staggering. The motivations for people to volunteer as community health workers have previously been well described and include both financial and non-financial reward [488, 489] [283]. However, the factors that influence how a family member or friend becomes a volunteer carer, or 'guardian', are less well understood. This study goes some way to describing those factors. Although a few guardians felt pressure from the patient or other family members to take on the role, the vast majority felt some duty to care for the person who was sick which was instinctive and entirely intrinsic within themselves. Occasionally, guardians were motivated by the fear that the community would think badly of them if they did not step up to the task; or the hope that their good deed would be reciprocated in the future.

There were a few instances where people encountered discrimination, but this was not a central theme and the examples were all related to fears around TB being associated with HIV, which have been well illustrated in previous studies [467, 469, 472, 475, 490-492]. Specifically related to TB retreatment, it was acknowledged that admission to hospital often disclosed HIV as well as TB status, particularly if the admission was long. The situations of the communities in this study is likely to be of significance in understanding this - the research was conducted in two urban areas with high burdens of HIV and TB where awareness about the two conditions is high. Therefore the understanding and assumptions which people are able to make may apply less so in settings where the prevalence of HIV is lower. Importantly, there was only perceived, but not realised, discrimination around guardians delivering injections in the community, and there was no perceived or realised stigma attached to injecting at home.

7.6.3 Emotional experience

Emotionally, there was a broad range of experiences, which arose from medical, practical and social factors. Experiences of people on the ward were often distressing, with issues around overcrowding, lack of space, and hygiene being paramount. Other common feelings were the sadness and anxiety around financial

issues and the neglect of children at home, which is consistent with previous literature [493].

The psychological effect of illness and hospitalisation on patients was clear. Although essentially a social phenomenon, 'the sick role' has been categorised as an emotion in this context because it is being used to refer to the patient's *feeling* of being maintained within a sick role. The concept was first described by Talcott Parsons in 1951 [494], and developed since then [495-497]. He described illness as not simply a biological or physiological phenomenon, but also a social and cultural one, in which the sick person adheres to a specific role within society. This role brings with it certain rights and responsibilities. The rights of the sick person are that they are exempted from certain social duties and responsibilities, and that they should not be seen as responsible for their illness. Obligations of people who have adopted the sick role include recognising that the state of illness is not desirable and wanting to get well, as well as actively seeking help and engaging in a relationship with medical professionals. Data from this study clearly demonstrate patients taking on a sick role, as the nature of their position in society and relationships with others are completely changed by their illness. There is a clear difference in the extent to which patients in hospital and in the community take on this role. Moreover, one of the aspects of community-based care which contributed most to patients emotional well being (and, according to some, physical well being) was the ability to practically and psychologically move away from this role.

7.6.4 Medical care and the health system

Experience of medical care varied. Participants described well known barriers and facilitators to accessing care such as previous experience of TB [200], costs [274], accessing informal providers [473], stigma [468], and HIV [498].

For both hospital and community-based care, trust in the health system is crucial. Theories of trust, as described by Giddens and Luhmann, can be framed around both trust in the individual (interpersonal trust) and in the system (institutional

trust)[499, 500]. The importance of trust in the health system is that it increases a patient's willingness to seek care, enhances ability to engage with treatment, improves relationships between patient and clinicians, facilitates disclosure by patients, enables necessary behaviour change and may grant patients more autonomy in decision-making [501]. Gilson argues that trust underpins the co-operation amongst people necessary to achieve a common goal [502]. She goes on to suggest that respectful treatment of patients by healthcare professionals is crucial in developing trust, and that central components of that respect include positive attitudes and behaviours, thoroughness and technical competence [503]. Similarly, Mechanic reports that 'interpersonal competence,' comprising caring, concern and compassion, is the most common aspect of trust in health care amongst patients with serious illness [504]. In the current study we see that indeed trust in the healthcare system was primarily determined by interactions with healthcare workers, and that failure of these representatives to earn the respect of trial participants, for example by not changing a drip in time or by 'shouting' at guardians, impaired the relationship between the two. Conversely, the feeling of security generated by being in hospital represented the trust that people had in the ability of clinicians and nurses to provide help if a patient was unwell. Likewise the fact that participants agreed to take part in the trial demonstrates that not only did participating patients and guardians have trust in each other, but also that a relationship had been developed in which they trusted that they would be able to access care from health workers should they need it. In fact, some of the reasons provided for *non-participation* came from those who did *not trust* that the system would come to their assistance if there was a problem at home.

One of the major advantages of community-based care was the opportunity to escape the overcrowded and often unclean conditions on the ward. The distress that this caused to patients and guardians is in keeping with previous literature in which patients with MDR-TB have expressed a preference for home-based care, siting transmission of infection and lack of psychosocial support as problems with hospital-based care [505].

7.6.5 Study limitations

The study had some limitations. Data were collected almost exclusively at a single time point, just after completion of injections. It may have been that experiences changed during the period of the intervention and also that community-based management may have longer term effects on participants beyond the completion of injections. Although observations were conducted during the intervention phase, longitudinal data throughout the intensive phase of treatment and after it's completion may have provided additional insights, allowing the development of increased rapport between participants and researchers, and thereby enabling more detailed exploration of experience. Additionally, although every attempt was made to sample participants who experienced adverse events during the trial, only two participants (one patient and his guardian) were interviewed who had complications whilst in the community. Particular focus was paid to the data provided by these participants however it may have been possible to get more understanding of the potential negative consequences of community-based care had there been other interviewees who had experienced significant difficulties. The impact of urban or rural residence and was not specifically examined in this study. Only three of the interviewees were from rural areas and their experiences did not seem to differ significantly from other participants, although data from other participants not living in the city may have revealed more subtle differences in experience. This study was not exempt from the inherent difficulties of collecting observational data, including the observer altering behaviour by their mere presence and the ethics of collecting data without full informed consent. However, data were collected in the most unobtrusive way possible without misleading patients, guardians and staff.

7.6.6 Stakeholder concerns addressed

There had been a number of concerns raised by those consulted at the start of the TB-RROC trial, which this evaluation have helped address. Firstly, there was a fear that guardians simply would not deliver the injections at home. These qualitative

data back up the quantitative data from the trial, which suggest that adherence to injections was exemplary. Not only did trial participants report excellent adherence, this was made more convincing by the (often in-depth) explanations they were able to provide as to why they would not miss doses; and clear descriptions of the duty they felt to complete the task they had taken on. There were however, a small number of instances where situations developed in which a dose might have been missed, but in each case the issues were resolved and injections were delivered on schedule.

Secondly, there had been a worry that guardians would not be competent to deliver injections. Indeed, many patients and guardians were also initially apprehensive. However, all of those who took part in the study were able to overcome these concerns, embrace the responsibility, and even be proud of what they had achieved. This experience has been reported in other settings, for example Livermore et al [506] quote a parent taught to administer injections for rheumatoid arthritis to their child as saying "I felt a sense of achievement. I have never wanted to be a nurse or give injections, but to keep him in his normal pattern of school, I will do anything." The one occasion where complications around injections did arise seemed not to be directly related to the ability of the guardian to do the injection, but more to the condition of the patient. All other accounts from patients as well as guardians demonstrated that, once trained, guardians giving injections was 'just the same.'

Thirdly, the issue of access to medical care during treatment at home had been raised. Very few participants described needing to access care whilst in the community but those who did were able to contact the study team, and in the one situation where admission was necessary, this was easily arranged and the ultimate outcome was positive. There was, however, a clear recognition that community-based management was not for everyone, and only those well enough should be selected for discharge.

Finally, it had been suggested that training people to do injections might create a cadre within society of 'lay injectors' who would be expected to provide injections for people within their communities. The data from this study strongly suggest that the risk of that happening would be very low. Guardians had a very clear understanding of the limitations of their role, and strongly rejected the idea of injecting people other than their own patient without instruction from the hospital. On the other hand, they would be keen to put their newfound skills to use by helping others in the future, under supervision from the health system.

7.6.7 Conclusion

Overall, these data demonstrate that the experience of community-based management offers many advantages over hospital-based management. Concerns raised by participants as well as stakeholders have been both recognised and addressed. Although there were abstract worries about issues in the community such as adherence, relationships between patients and guardians and the ability of lay people to deliver injections safely, none of these were borne out in real experiences. Community-based management offers a number of benefits, including fewer financial difficulties, improved emotional well-being, and the ability to continue social interactions and daily activities.

> *"That part [performing injections] needs to be fulfilled by the nurses because it is their job. But a guardian does this job because people can't stay in the hospital for 2 months … it is a place where you end up getting other infections instead of getting well … you find that most of your relatives are not able to go there because of financial constraints … they saw it was possible for a guardian to go and inject a patient at home if properly trained. They saw it was a good idea."*
>
> P15, Female guardian

8 Final discussion and recommendations

This thesis presents an in-depth assessment of the serious issues facing people with recurrent TB and their households in Malawi, and offers new approaches to alleviate some of those problems. People prescribed retreatment regimen make up only 11% of the total number of those prescribed TB treatment each year, and are therefore often overlooked in the clinical, research and policy arenas. The issue of tuberculosis recurrence features in the medical literature, but research falls almost exclusively into one of three categories: strategies to reduce the rate of relapse after initial treatment; how to identify patients at risk of MDR-TB; and, less frequently, presentation of data demonstrating the high proportion of unsuccessful treatment outcomes on WHO Category II regimen. These are no doubt central issues facing TB control and management, and should remain a focus of attention, however this thesis clearly demonstrates that TB retreatment is associated with a hugely disproportionate burden of clinical, social and economic problems. If targets to reduce death from TB and eliminate catastrophic costs associated with treatment are to be met, it will therefore be necessary to broaden the agenda and begin to address the specific issues faced by people on retreatment.

The final chapter of the thesis will summarise the key findings of the research, discuss their implications, and present ideas for future work. Two main issues facing adults on TB retreatment were identified and addressed. Firstly, clinical outcomes on retreatment are poor. Although this issue is frequently reported, there are few data examining the reasons for poor outcomes, so ideas about *how to improve outcomes* are lacking. Secondly, patients on retreatment regimen require injections of streptomycin daily for the first two months of treatment, and so currently in Malawi have to suffer the consequences of long term hospital admissions. Although many models exist for community-based management of patients on first-line treatment and treatment for MDR-TB, few specifically address the issue *of how to deliver injectables* during the intensive phase.

It was intended that this piece of work provide a comprehensive evaluation of the management of TB retreatment in Malawi, therefore the approach was informed by realist theories of evaluation [301]. As such, chapter 3 reports a cohort study which describes the clinical context of retreatment, following which four chapters evaluate the new model of delivering care within that context. After reviews of the literature and development of the model with relevant stakeholders, the evaluation of this complex intervention began with a pilot study, and then employed a mixed methods approach to examine the mechanisms and outcomes of the new model of community-based care.

8.1 The clinical context: Exploring reasons for poor clinical outcomes on TB retreatment in Malawi

A prospective cohort study was conducted at QECH in order to investigate why treatment outcomes on TB retreatment in Malawi are poor. The study recruited 158 patients and the key messages are summarised in Box 1. The findings of the study are in keeping with previous reports of low rates of successful completion on the WHO Category II regimen (see chapter 1). They also suggest that factors other than drug resistance are responsible for these poor outcomes, such as chronic lung disease, HIV, ART failure, renal disease and anaemia.

There are a number of areas where interventions may have the potential to reduce morbidity and mortality. Firstly, the issue of chronic lung disease needs to be addressed. This was recently highlighted by Metcalfe et al, who reported that 74% of patients on retreatment regimen had abnormalities on plain chest x-ray consistent with chronic lung disease, and concluded that “retreatment of tuberculosis in the modern era represents a common pathway for individuals with chronic lung disease who remain symptomatic after repeated interactions with the public health system … empiric treatment exposes patients to drug toxicities and increased health-care costs without benefit” [507]. One of the main obstacles in tackling chronic lung disease in resource limited settings is the lack of available

diagnostic tools. Even in the most affluent settings, the diagnosis of bronchiectasis is complex and can only be made accurately using CT [508]. This study has shown once again that CXR is an inadequate method for diagnosing bronchiectasis, but suggests that spirometry may be useful. Spirometry can now easily be used away from central hospitals and its use is advocated in the WHO's 'Practical Approach to Lung Health' for the diagnosis of respiratory disease at all levels of the healthcare system [509]. Postural drainage of respiratory secretions is a technique which requires no equipment and could be easily implemented with very limited requirement for materials and some basic training. A slightly more complicated issue to address is the problem of antibiotic management of bronchiectasis. This depends very much on the spectrum of pathogens involved in colonisation of the airways and infective exacerbations [510, 511]. Further information concerning the microbiology of bronchiectasis in post-tuberculous lung disease in high TB burden settings would help to design appropriate algorithms for the management of infection where sputum culture is not routinely available for bacteria implicated in bronchiectasis.

Box 1: Key findings in the TB-RROC cohort study

- Clinical outcomes on TB retreatment regimen in Malawi are still poor: only 68.4% successfully complete treatment, and mortality is 24.1%.
- Drug resistance in patients with recurrent TB in Malawi is uncommon: 90.4% of patients are infected with a fully sensitive strain of *M. tuberculosis.*
- Hypotension at baseline is associated with poor clinical outcome.
- Medical co-morbidity is common in patients on TB retreatment in Malawi. Chronic lung disease, HIV, ART failure, renal impairment and anaemia are highly prevalent.
- Streptomycin toxicity is common in patients on TB retreatment in Malawi: 35.9% of patients develop ototoxicity and 14.6% develop nephrotoxicity.

The second area for targeting interventions to improve mortality in patients with recurrent TB is HIV. Although the interaction between TB and HIV is well studied and routinely addressed in the delivery of care, the management of patients with recurrent TB poses specific challenges. The burden of HIV seems to be higher in this group of patients. Because HIV positive people will be living longer on ART they will be at increased risk of recurrent episodes of TB. In high TB high HIV burden settings, this may result in both increasing numbers of people getting recurrent TB, and increasing HIV prevalence in that group. Additionally, as people live longer on ART they will be at increased risk of both ART failure and recurrent TB, which is likely to result in a high prevalence of ART failure in patients on retreatment, as was seen in this study. Key recommendations for settings such as Malawi therefore reiterate the importance of testing all patients with TB for HIV, but also that viral load testing and second-line ART are made easily available at centres treating patients with recurrent TB.

The incidence of streptomycin toxicity was high, with ototoxicity being particularly common. Streptomycin is the oldest anti-tuberculous drug, yet surprisingly little is known about it. Very few data exist about the pharmacokinetics of the drug, and dosing schedules are not based on good evidence [512]. Monitoring for toxicity and taking steps to reduce the impact of hearing loss and kidney damage are important. However, it is also necessary to explore possible avenues to reduce the risks of adverse drug reactions all together by understanding their mechanisms and devising regimens which limit the risk of toxicity.

Patients with recurrent TB are a sick group, presenting with hypotension, renal impairment, severe lung disease and anaemia. Therefore the management of patients on TB retreatment relies on many of the same resources which are required to manage all acutely sick patients. In order to properly care for any severely unwell patient, it is necessary to have access to basic blood tests such as serum creatinine, to have the facilities to give blood transfusions to patients with severe anaemia, to resuscitate hypotensive patients, and provide oxygen to patients in respiratory distress. This requires not only material, but human resource.

Once again, it is seen that disease specific interventions can only go some way to improving treatment, and that without approaches which strengthen and develop whole health systems it will be hard to deliver better care [513, 514].

8.2 A new mechanism: Community-based management for delivering injectables in TB retreatment

In order to reduce the burdens of in-patient management for TB retreatment, an intervention which involved training guardians to deliver streptomycin to patients in the community was evaluated. Mixed methods used to assess the intervention included a pragmatic clinical trial of hospital versus community-based care; a health economic evaluation; and a qualitative study examining the experiences of study participants. The main findings of the evaluation are summarised in Box 2.

Box 2: Key findings in the evaluation of the TB-RROC trial

- Of patients who received community-based management during the intensive phase of TB retreatment, 93% successfully completed 2 months of treatment, compared to 96% who received hospital-based management (risk difference -3%; 95% CI -9% - 3%).
- The proportion of patients who successfully completed TB treatment at 8 months did not differ according to model of care received during the intensive phase.
- There were no deaths or serious adverse events in the community directly related to guardians administering streptomycin.
- Community-based management during the intensive phase of TB retreatment was cost effective for both providers and users.
- Community-based management during the intensive phase of TB retreatment significantly reduced the risk to households of catastrophic health expenditure.
- Community-based management offered many social advantages to patients, guardians and households affected by recurrent TB.

The first domain which the evaluation aimed to examine was the clinical one, in which health outcomes were assessed in patients who received streptomycin from guardians at home. The randomised clinical trial demonstrated that outcomes at two months were similar for community-based and hospital-based management, but that community-based management was not statistically non-inferior at a 6% margin. Although there were some serious adverse events in the community arm, the number was similar to that in the hospital arm and none were directly related to guardians giving injections – there were no infections, sciatic nerve palsies or needle stick injuries in the community. Descriptions provided in the qualitative evaluation also suggested that once trained, guardians were entirely competent to administer injections safely: *"… but I saw it was just the same as over the two weeks I had been in hospital and was injected by the doctor. There wasn't any difference."*

Nevertheless, the TB-RROC cohort study has already emphasised that this intervention was delivered in the context of patients with multiple and complex medical problems. It must therefore be acknowledged that a possible disadvantage of community-based care is that these patients benefit from being in hospital precisely because they have multiple clinical needs beyond simply their current TB episode. A strong message from study participants and healthcare workers was that community-based management should only be offered to patients who are well enough to be managed away from the hospital and that clear procedures are in place for readmission should a patient deteriorate whilst at home. During the trial there were a total of 11 readmissions to hospital from the community and only one patient died at home (after an acute severe illness lasting less than one day), suggesting that overall participants were able to access care if they did become unwell in the community.

Methods of care delivery during the intensive phase did not seem to affect overall 8 month treatment outcomes, with 77.2% of patients managed in hospital having successful treatment outcome and 80.7% of patients managed in the community having successful treatment outcome. Default rates were low in both arms of the

study, but the qualitative evaluation did provide evidence to support the theory that participants became more engaged with their care if given the responsibility of having injections at home, as one study participant described: "*They say doing injections is for healthcare workers, but when doing this work it is like we are saying that this problem is for everyone and everyone at home will receive it with both hands."*

The concern that adherence to injections in the community would be a problem was expressed by members of the NTP, CAB and other researchers. However, the data from the trial show that there were no patients who defaulted from treatment in the community, and very few missed doses of streptomycin. Once again, this experience is backed up by the qualitative evaluation, in which it was found that although concerns were expressed about adherence, particularly if the guardian was in a position of less influence than the patient, there were no instances where patients or guardians did not adhere to treatment.

The second domain which was evaluated was the economic impact of retreatment in the hospital and in the community. The repercussions of hospital-based care for already precarious financial situations of households was a major theme in the qualitative evaluation, and reducing these consequences was seen as a major advantage of community-based care. Admission to hospital frequently had devastating consequences for peoples livelihoods: *"I was the one responsible for running the affairs of the household, and I was also the same person who got sick. Therefore everything seemed to stop."* The quantitative economic evaluation demonstrated that community-based management reduced the absolute user costs during the intensive phase from US$ 271.6 to US$ 101.8, and the risk of incurring costs >20% annual household income from 62% to 11%. It was also shown that the benefits of community-based care in terms of reducing catastrophic health expenditure were seen in different groups and were independent of wealth, HIV status or gender. Overall, the intervention was cost effective, reducing the cost per patient successfully completing 2 months of treatment by US$ 817.

Finally, social impacts of the intervention were examined, primarily by the qualitative evaluation of the trial. The qualitative evaluation provided data which illustrated the huge sacrifices made by families and communities in order to care for patients admitted to the hospital. Escaping the overcrowded and often unhygienic conditions on the ward in order to go home and be able to go to work, look after children, socialise with friends, attend school and church was a major theme and highlighted some of the advantages of community-based care.

Limitations of the individual components of the evaluation have been addressed in the relevant chapters, however there are some general issues which are worth discussing. Firstly, the evaluation was carried out in only two sites, both of which are urban centres in Malawi. Although Bwaila hospital is technically a district hospital, it is very much situated in the context of the capital city and therefore has many similarities with a central hospital, such as access to investigations and levels of staffing. Further information may be gained from additional sites based in truly more district settings. Secondly, the evaluation was done mostly at a limited time point. This applies to the trial whose primary endpoint was at 2 months, although data were also collected for a large group (162/204 patients) who completed treatment during the time that the study was still open. However, it also applies to the economic evaluation in which it was not possible to formally estimate provider costs at 8 months; as well as to the qualitative evaluation which only interviewed participants at a single time point soon after completion of the intervention. Thirdly, although some of the issues of 'what worked for who and why?' were able to be addressed in the economic and qualitative pieces, the clinical trial was not large enough to examine these questions by performing sub-group analyses.

8.3 Research outcomes: Recommendations and future work

Drawing on the findings from all aspects of this evaluation, it is possible to suggest some modifications to the model of community-based management, which may improve it's implementation:

1. Eligibility of patients for community-based care

In the intervention, patients were considered for community-based care if they were 'declared fit by a clinician,' with no criteria more specific than that a clinical assessment was required. Stakeholders, trial participants and key informants all recognised the importance of discharging people only once they were 'strong enough.' Data from the cohort study highlight the complex medical problems which patients have. Discussion with clinicians and nurses involved in the trial and working on the wards during the period the trial was running also highlighted the importance of ensuring patients were well selected for community-based management. Together, these experiences suggest that the criteria for discharge should be more specific and not rely solely on the judgement of a single clinician. For example, a checklist could be developed which would make sure that certain basic medical criteria are met prior to discharge. Such medical criteria might include having had certain investigations (full blood count, CXR, HIV test, HIV viral load if appropriate, sputum GXP), as well as meeting basic clinical criteria such as having normal blood pressure, respiratory rate and body temperature. This would go some way to both ensure and document patients' fitness, and also to reassure patients and guardians.

2. Eligibility of guardians for community-based care

During the trial, the choice of guardian was left entirely up to the patient. It was felt that a patient would be the best judge of who would be able to look after them, and that if the patient chose their guardian the relationship between the two would be strong. However, it is clear, particularly from the qualitative data that the process of choosing a guardian and the factors that influence motivation to become a guardian were varied and complex. Most patient-guardian relationships worked extremely

well, but there were a small number of situations where the relationship broke down, even if only temporarily. Ultimately, the process of recruiting participants in a community-based intervention will begin with identifying a patient on treatment. Therefore, they will remain the first and primary point of contact with healthcare workers. Nevertheless, the data suggest that a more structured approach to supporting patients in identifying a suitable guardian may be useful. Healthcare workers might encourage patients to examine certain issues in their choice of guardian, for example:

- What is the relationship between patient and guardian?
- What is the age difference between patient and guardian?
- Where does the guardian live in relation to the patient?
- How will taking on injections affect the guardian's work?
- Does the guardian drink alcohol?
- What will happen if something goes wrong?

A checklist for choosing a guardian is unlikely to be successful because individual situations are specific, very varied, and often dependent on people other than the patient. However, the patient remains at the centre of the experience, and an informal process may help to ensure they chose the most appropriate guardian wherever possible.

3. Training of guardians

The training to do injections seemed to work well for all guardians. Initial fears were laid to rest during the process of learning how to do injections. The only suggestion for improvement of the training process came from a number of patients who requested that they should be present during the training. This recommendation should easily be implemented, and in fact was applied as an adaptation to the training process during the course of the trial.

4. Accessing medical care from the community

The problem of accessing healthcare if a patient's condition deteriorates is a disadvantage of community-based management that must be acknowledged and accepted. However, it is important to both minimise the risks and to allay the fears which being out of hospital generate. Not only is it crucial to ensure adequate mechanisms for community follow up and medical management, it is essential that patients and guardians understand that they are still under the care of the health system, and that there are clear, practical and realistic processes by which they can access care.

The results of the TB-RROC evaluation can be summarised by saying that in the Malawian context clinical outcomes are probably not worse for patients who receive community-based care during the intensive phase of TB retreatment, that community-based care offers a cost-effective alternative to hospital-based care, and that there are economic and social benefits for a broad range of participants. The next stage involves considering the application of these findings within an operational situation. Ultimately, it is up to decision-makers to determine if community-based management is of benefit to the populations they provide for. Discussions with the Malawi NTP are on-going, and it has been suggested that the intervention should be evaluated under operational, rather than trial conditions, by performing a limited 'post implementation' study in Blantyre and Lilongwe.

The TB-RROC intervention offers an entirely new model for delivering intramuscular injections as part of long-term treatment for tuberculosis in low resource settings, and has the potential to have application in different contexts. Currently, many NTPs are struggling with the issue of how to deliver care to the growing number of people requiring treatment for MDR-TB. Although the recommendation is for community-based management [157], there is not an obvious approach to the component of community-based care which involves providing daily intramuscular injections. Published schemes have involved either nurses travelling to patients homes, or patients travelling to the health facility [288], both of which require significant expenditure for either the health system or the patient on transport and

time. This new model, which involves training people who are in regular close contact with patients in the community to administer injections, has the potential to offer a more efficient and less costly alternative for patients with MDR-TB as well as those on retreatment regimen.

8.4 Final conclusion

As a whole, this piece of work has demonstrated the broad range of difficulties posed by the current 'retreatment regimen.' Category II regimen has no clinical trial evidence base, is associated with poor treatment outcomes, high rates of toxicity and the problems which accompany having to provide intramuscular injections. Yet it is still recommended by the WHO and used in the majority of low and middle income countries worldwide which have high burdens of recurrent TB in conjunction with the poor access to DST. There is an urgent need for this regimen to be re-evaluated, particularly with respect to the use of streptomycin. Few data exist on which to base decisions about the use of streptomycin, however those available do suggest that patients infected with an isoniazid resistant strain of M. tuberculosis have better clinical outcome if they receive streptomycin as part of their regimen [67]. As isoniazid resistance is the commonest non-MDR resistance pattern globally as well as in the recent MDR-TB survey in Malawi, and that it probably has the most impact on clinical outcome, streptomycin is still recommended for patients with recurrent TB in whom the prevalence of isoniazid resistance is of greatest concern. It is for these reasons that at a meeting of the Malawi TB technical working group in May 2015 it was decided to continue using the WHO category II regimen, and that WHO guidelines still recommend the regimen where access to DST is poor and the prevalence of MDR-TB is low.

In summary, this thesis has drawn attention to the broad range of challenges faced by patients in Malawi with recurrent tuberculosis. It presents a comprehensive, prospective cohort study which, for the first time examines the burden of co-morbidity in patients entering care at the point of a recurrent TB episode, and in so

doing identifies areas in which interventions may improve clinical outcomes for this group of patients. It also evaluates an entirely new method of delivering injectable agents as part of TB care in low resource settings. In the Malawian context, clinical outcomes are probably similar for patients who received hospital and community-based management. However, community based management is associated with lower costs to the health system and better economic outcomes for users through mechanisms such as limiting food expenditure and reducing lost earnings; and with improved social outcomes through mechanisms such as maintaining dignity, independence and the ability to continue playing useful roles within family and community groups. Community-based management in which injections are delivered by trained guardians offers a new model of care which has the potential to benefit patients with MDR-TB as well as the thousands of patients treated for recurrent tuberculosis each year.

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10 Appendices

10.1 TB-RROC Community Advisory Board

10.1.1 TB-RROC CAB Terms of Reference

1. What is a Community Advisory Board (CAB)?

A CAB is a group of volunteers whose role is to act as a liaison between a research organisation (such as MLW) and participant communities. The members of the board provide perspectives from the participant communities on the research work that is carried out by the organisation.

2. What are the functions of the CAB?

A CAB has the following major functions:

- Assisting in the planning and implementation of research activities including study feasibility, recruitment, community education and community acceptability.
- Providing feedback about community concerns and opinions.
- Advising on best outreach and education methods to ensure communication between the research organisation and study participants.

3. Who are the members of the CAB?

- Membership of a CAB is strictly voluntary.
- The members of a CAB should consist of members of the community in which the research is carried out.
- Members should:
  - Be active in the community
  - Be chosen by the community members
  - Have an interest in health related issues
  - Be culturally sensitive
- The CAB will consist of 6 – 8 members.
- The CAB will elect one chairperson.
- Introductory training will be provided for all members of the CAB.

4. What responsibilities do CAB members have?

- Members of the CAB agree to strictly adhere to all legal and ethical standards regarding medical confidentiality. Membership of the CAB may be terminated if there is any breach in confidentiality.
- Members of the CAB agree to give attention to mail and telephone calls from the responsible research team.
- Members of the CAB agree to serve for the duration of participant recruitment into the study (from 2013 until 2015).
- Members of the CAB should attend all meetings. A member may be dropped from the Board if they miss three consecutive meetings.

5. How often does the CAB meet?

- The CAB will meet approximately once every three months.
- There will be a seating allowance for each meeting attended. This will be in-line with MLW rates and policies.

6. How does the CAB make decisions?

- Not every issue discussed at CAB meetings requires a decision to be made; however when a decision is required, voting may be carried out.
- In the event of a vote, each member will have one vote and the outcome will be decided based on a simple majority. At least five members will be need to be present for any formal decisions to be made by the group.

10.1.2 TB-RROC CAB minutes of first meeting

Date: **16th January 2013**
Venue: **MLW**
Present: **All 6 CAB members, Trial PI, Trial nurse, MLW Science Communication officer**

The following questions were raised by members of the CAB and discussed:

- How will guardians be identified?
  Patients will identify a guardian who they would like to be trained. The guardian must be available to inject daily for 60 days. The patient can chose to have a guardian who is not the one currently staying with them in the hospital. If the guardian is not competent to do the injection, the patient will have to stay in hospital. If the guardian goes away, the patient will have to come back into hospital. It will not be practical to train more than one guardian at the moment, but this suggestion will be kept in mind.

- What are the training procedures?
  The CAB was shown the training materials and reviewed the training procedures.

- How will streptomycin be stored and supplied?
  Streptomycin does not require refrigeration. It is not appropriate for the study to provide streptomycin, as drug procurement through the NTP is a key principle of the DOTS approach to TB control.

- How will the safety of guardians be ensured?
  In the unlikely event of a needlestick injury PEP will be provided if necessary. Practical and emotional support will also be provided during regular reviews by the study team. The intervention poses no additional risk in terms of TB transmission, but standard contact tracing procedures under the existing TB systems will be followed.

- How will the community be sensitised to the study?
  Suggestions included posters in health centres and meeting with TB officers, both of which are in the process of being organised.

10.1.3 TB-RROC CAB minutes of second meeting

Date: **19th June 2013**
Venue: **MLW**
Present: **All 6 CAB members, Trial PI, Trial nurse, MLW Science Communication officer**

Results of the pilot study and plans for the next stages were presented to the CAB, following which a number off issues were discussed:

- If 17 guardians successfully completed training in the pilot study, why were only 10 patients sent home?
  This was a pilot study which was trying to ask 2 questions: 1. Can guardians be trained to do injections? 2. Is it unsafe for guardians to give injections at home. In order to answer the first question, we trained all the guardians who were on the ward at the time. In order to answer the second question, we specified beforehand that only 10 patients would be discharged.

- What challenges were faced in the pilot study?
  The biggest challenge was the inconsistent supply of streptomycin. This made it difficult to predict what was going to happen day to day. Stocks have been good for the past few months and we are confident that this will not be a continuous problem.

- What changes have you made to the main study following the pilot study?
  1. Because recruitment was slower than we predicted, we have slightly changed the way we recruit patients. Initially patients were going to be recruited to the trial and the cohort study at the same time. Now patients can be recruited to one or both. If a patient does not have a guardian this does not mean that they should be excluded from the cohort study because the cohort study is trying to describe the clinical problems of ALL patients who get TB retreatment regimen.
  2. Because recruitment was slower, we have also reduced the target sample size to 268.
  3. We have made some small changes to the data collection forms so that is easier to collect accurate data for the main trial.

- What were the qualifications and education levels of the guardians in the pilot study? Can illiterate people be trained to do injections?
  We did not formally document the education level of the guardians (but will do so in the main study – see the point above!). However we know from talking to the guardians that most were illiterate and had not completed school. This did not seem to affect their ability to learn how to do the injections. Practical instruction is given with visual aids.

- Did you visit those 10 people who went home in the pilot study?
  Yes, we visited 1, 3 and 5 weeks after they were discharged home.

- Will you be providing food for patients who go home? In hospital, people are provided with food, but if they go home they will miss out on this.
  We are very aware of the problems of food for TB patients. However, many patients in hospital chose to have their own food rather than hospital food. This was not a concern raised by any of the participants in the pilot study. The benefits of being at home seem to far outweigh the benefits of hospital provided food.

- Question from the study team to the CAB: What is the best option for reimbursing transport money? Should it be a flat rate to avoid confusion, or according to distance travelled?
  Definitely according to distance travelled, plus a bit more (which should be the same for all distances). The study team will draw up standard travel costs.

- After the meeting, refreshments were provided and the CAB had a chance to talk informally to one of the patients who participated in the pilot study about her experiences of receiving injections given to her daily at home by her sister.

10.2 Radiology reporting proformae

10.2.1 Chest x-ray: descriptive

41179

Form RROC_X1 Chest X-ray report TB - RROC study

Study ID _____ **Date** DD MON YYYY

Description					
X102	qual	Radiograph quality	Optimal (1)	Suboptimal (2)	Uninterpretable (3)
X103	cons	Consolidation?		Yes (1)	No (2)
X104	conszone	If yes, which zones are affected? (mark all)		Left upper (1) / Left middle (2) / Left lower (3)	Right upper (4) / Right middle (5) / Right lower (6)
X105	consxtent	If yes, extent	Segmental (1)	Lobar (2)	Multifocal (3)
X106	gglass	Ground glass opacification		Yes (1)	No (2)
X107	gglassdis	Ground glass distribution		Perihilar (1)	Diffuse (2)
X108	cav	Cavitation		Yes (1)	No (2)
X109	mycet	Mycetoma		Yes (1)	No (2)
X110	vol	Volume loss		Yes (1)	No (2)
X111	volzone	If yes, which zones are affected? (mark all)		Left upper (1) / Left middle (2) / Left lower (3)	Right upper (4) / Right middle (5) / Right lower (6)
X112	volseg	If yes, which segments are affected? (mark all)	Lobar (1)	Segmental (2)	Subsegmental (3)
X113	retic	Reticular interstitial pattern?		Yes (1)	No (2)
X114	reticzone	If yes, which zones are affected? (mark all)		Left upper (1) / Left middle (2) / Left lower (3)	Right upper (4) / Right middle (5) / Right lower (6)
X115	reticdist	If yes, what is the distribution? (mark all)		Perihilar (1)	Peripheral (2)
X116	reticpat	If yes, what is the pattern?		Diffuse (1)	Random (2)
X117	honey	Honeycombing present?		Yes (1)	No (2)
X118	nod	Nodular pattern (<30mm)?		Yes (1)	No (2)
X119	nodpat	If yes, what is the pattern?	Single (1)	Diffuse (2)	Random (3)
X120	nodfeat	If yes, any special features? (mark all)	Cavitation (1)	Calcification (2)	Miliary (3)
X121	mass	Mass (>30mm)?		Yes (1)	No (2)
X122	masssing	If yes, single or multiple?		Single (1)	Multiple (2)
X123	bronch	Bronchiectasis?		Yes (1)	No (2)
X124	bronchdist	If yes, what is the location? (mark all)		Central (1)	Peripheral (2)
X125	bronchvol	If yes, associated volume loss?		Yes (1)	No (2)
X126	sten	Central airway stenosis?		Yes (1)	No (2)

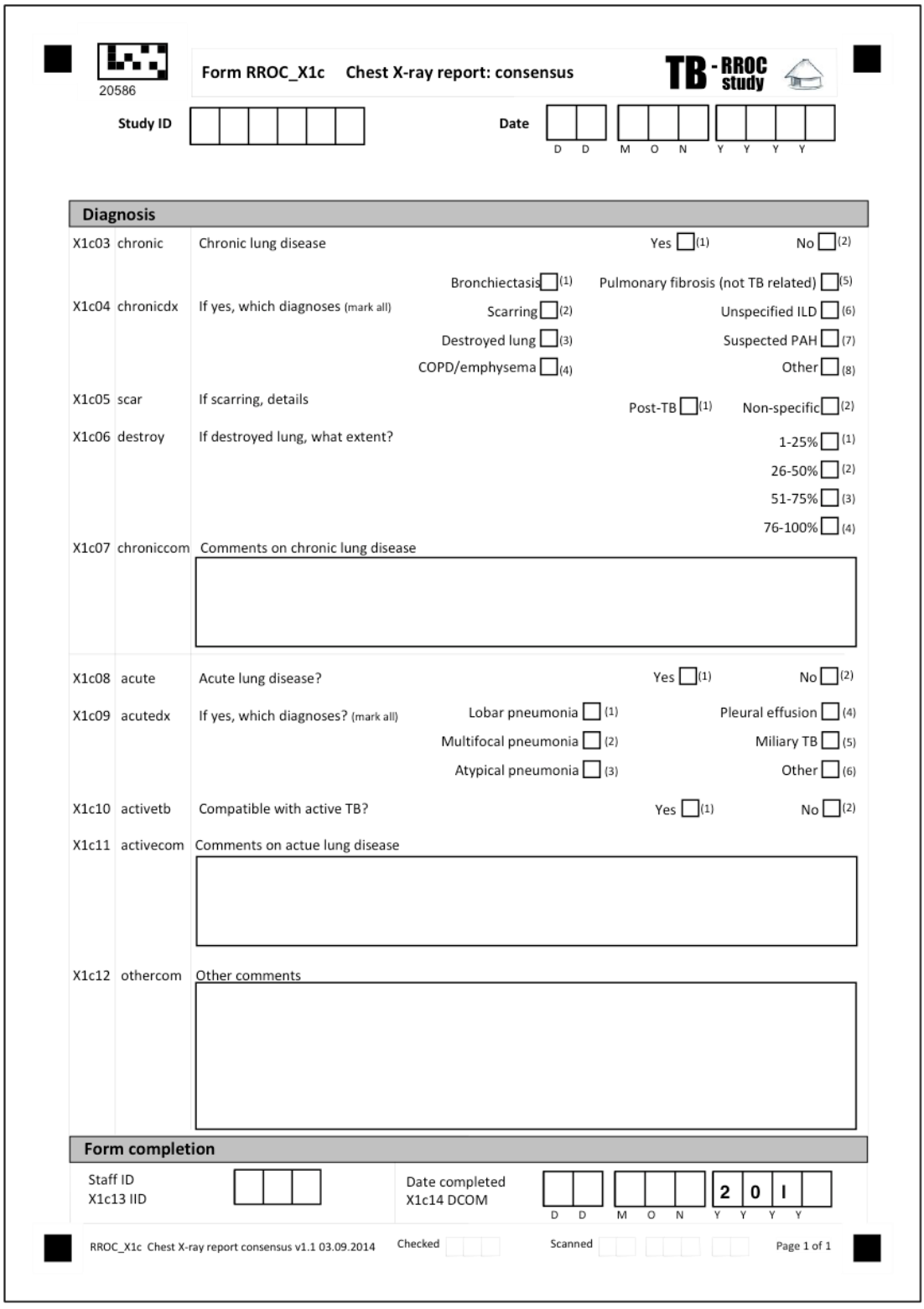
41179

Form RROC_X1 Chest X-ray report TB - RROC study

Study ID | | | | | | |

Description					
X128	hypinf	Hyperinflation?		Yes (1)	No (2)
X129	hypinfdist	If yes, distribution		Uniliateral (1)	Bilateral (2)
X130	hypinffib	If yes, secondary to fibrosis?		Yes (1)	No (2)
X131	bullae	Bullae?		Yes (1)	No (2)
X132	lynod	Lymphnode enlargement?		Yes (1)	No (2)
X133	lynodist	If yes, what is the distribution? (mark all)	Right hilar (1)	Left hilar (2)	Mediastinal (3)
X134	lynocalc	If yes, is there lymph node calcification?		Yes (1)	No (2)
X135	medmass	Mediastinal mass?		Yes (1)	No (2)
X136	pleff	Pleural effusion?		Yes (1)	No (2)
X137	pleffdist	If yes, distribution		Uniliateral (1)	Bilateral (2)
X138	plthick	Pleural thickening?		Yes (1)	No (2)
X139	plthickdist	If yes, distribution		Unilateral (1)	Bilateral (2)
X140	plthickloc	If yes, location		Apical (1)	Basal (2)
X141	plplaq	Pleural plaques?		Yes (1)	No (2)
X142	pneumo	Pneumothorax?		Yes (1)	No (2)
X143	cardiac	Enlarged cardiac shaddow?		Yes (1)	No (2)
X144	cardeff	Consistent with pericardial effusion?		Yes (1)	No (2)
X145	bones	Bones and chest wall abnormal?		Yes (1)	No (2)
X146	soft	Soft tissues (neck, axillae, abdomen) abnormal?		Yes (1)	No (2)

10.2.2 Chest x-ray: diagnostic



20586

Form RROC_X1c Chest X-ray report: consensus TB - RROC study

Study ID | | | | | | |

Date D D M O N Y Y Y Y

Diagnosis

X1c03	chronic	Chronic lung disease	Yes ☐ (1)	No ☐ (2)
X1c04	chronicdx	If yes, which diagnoses (mark all)	Bronchiectasis ☐ (1)	Pulmonary fibrosis (not TB related) ☐ (5)
			Scarring ☐ (2)	Unspecified ILD ☐ (6)
			Destroyed lung ☐ (3)	Suspected PAH ☐ (7)
			COPD/emphysema ☐ (4)	Other ☐ (8)
X1c05	scar	If scarring, details	Post-TB ☐ (1)	Non-specific ☐ (2)
X1c06	destroy	If destroyed lung, what extent?	1-25% ☐ (1)	
			26-50% ☐ (2)	
			51-75% ☐ (3)	
			76-100% ☐ (4)	
X1c07	chroniccom	Comments on chronic lung disease		
X1c08	acute	Acute lung disease?	Yes ☐ (1)	No ☐ (2)
X1c09	acutedx	If yes, which diagnoses? (mark all)	Lobar pneumonia ☐ (1)	Pleural effusion ☐ (4)
			Multifocal pneumonia ☐ (2)	Miliary TB ☐ (5)
			Atypical pneumonia ☐ (3)	Other ☐ (6)
X1c10	activetb	Compatible with active TB?	Yes ☐ (1)	No ☐ (2)
X1c11	activecom	Comments on actue lung disease		
X1c12	othercom	Other comments		

Form completion

Staff ID X1c13 IID | | | |

Date completed X1c14 DCOM D D M O N 2 0 Y Y

RROC_X1c Chest X-ray report consensus v1.1 03.09.2014 Checked Scanned Page 1 of 1

10.2.3 CT Thorax: descriptive

38292

Form RROC_X2 CT Thorax report TB - RROC study

Study ID **Date**

X203	qual	Scan quality	Optimal (1)	Suboptimal (2)	Uninterpretable (3)
X204	cons	Consolidation?		Yes (1)	No (2)
X205	conszone	If yes, which zones are affected? (mark all)		Left upper (1)	Right upper (4)
				Left middle (2)	Right middle (5)
				Left lower (3)	Right lower (6)
X206	consxtent	If yes, extent	Segmental (1)	Lobar (2)	Multifocal (3)
X207	gglass	Ground glass opacification?		Yes (1)	No (2)
X208	gglassdis	Ground glass distribution	Perihilar (1)	Diffuse (2)	Patchy (3)
X209	cav	Cavitation?		Yes (1)	No (2)
X210	mycet	Mycetoma?		Yes (1)	No (2)
X211	cyst	Cysts?		Yes (1)	No (2)
X212	vol	Volume loss?		Yes (1)	No (2)
X213	volzone	If yes, which zones are affected? (mark all)		Left upper (1)	Right upper (4)
				Left middle (2)	Right middle (5)
				Left lower (3)	Right lower (6)
X214	volseg	If yes, which sements are affected? (mark all)	Lobar (1)	Segmental (2)	Subsegmental (3)
X215	round	Rounded atalectasis?		Yes (1)	No (2)
X216	distort	Architectural distortion?		Yes (1)	No (2)
X217	retic	Reticular interstitial pattern?		Yes (1)	No (2)
X218	reticzone	If yes, which zones are affected? (mark all)		Left upper (1)	Right upper (4)
				Left middle (2)	Right middle (5)
X219	reticdist	If yes, what is the distribution? (mark all)		Left lower (3)	Right lower (6)
				Perihilar (1)	Peripheral (2)
X220	reticpat	If yes, what is the pattern?		Diffuse (1)	Random (2)
X221	honey				
X222	bands	Honeycombing present? Yes (1) No (2)	Parenchymal bands?	Yes (1)	No (2)
X223	nod	Nodular pattern (<30mm)?		Yes (1)	No (2)
X224	nodpat	If yes, what is the pattern?	Single (1)	Diffuse (2)	Random (3)
X225	noddist	If yes, what is the distribution (mark all)		Centrilobular (1)	Septal (2)
X226	nodfeat	If yes, any special features? (mark all)		Cavitation (1)	Halo (4)
				Calcification (2)	Ground glass (5)
				Miliary (3)	Other (6)
X227	mass	Mass (>30mm)?		Yes (1)	No (2)
X228	masssing	If yes, single or multiple?		Single (1)	Multiple (2)
X229	halo				
X230	revahalo	Halo sign? Yes (1) No (2)	Reverse halo?	Yes (1)	No (2)

RROC_X2 CT Thorax report v1.1 03.09.2014 Page 1 of 2

38292

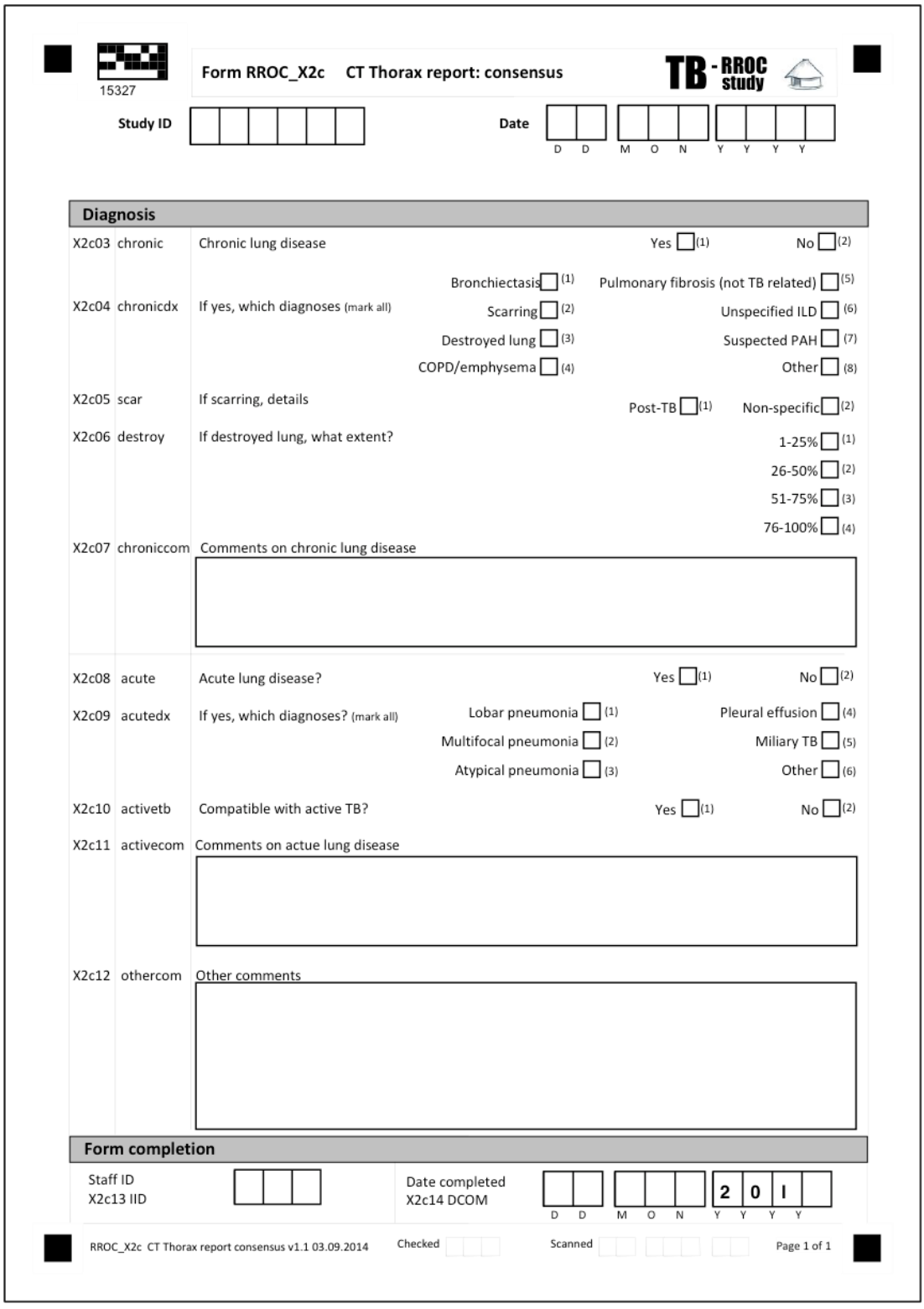
Form RROC_X2 CT Thorax report

TB - RROC study

Study ID ☐☐☐☐☐☐

X232	bronch	Bronchiectasis?	Yes ☐ (1)	No ☐ (2)
X233	bronchdist	If yes, what is the location (mark all)	Central ☐ (1)	Peripheral ☐ (2)
X234	bronchfeat	If yes, any special features? (mark all)	Volume loss ☐ (1)	Bronchiolectasis ☐ (4)
			Cystic change ☐ (2)	Post obstructive ☐ (5)
			Traction bronchiectasis ☐ (3)	
X235	airway	Any of the following airways features?	Bronchial wall thickening ☐ (1)	Central airway occlusion ☐ (4)
			Endobbronchial nodules ☐ (2)	Tree in bud ☐ (5)
			Central airway stenosis ☐ (3)	Mosaic attenuation ☐ (6)
X236	hypinf	Hyperinflation?	Yes ☐ (1)	No ☐ (2)
X237	hypinfdist	If yes, distribution?	Uniliateral ☐ (1)	Bilateral ☐ (2)
X238	hypinffib	If yes, secondary to fibrosis?	Yes ☐ (1)	No ☐ (2)
X239	bullae	Bullae?	Yes ☐ (1)	No ☐ (2)
X240	emph	Emphysema?	Yes ☐ (1)	No ☐ (2)
X241	emphdist	If yes, distribution?	Uniliateral ☐ (1)	Bilateral ☐ (2)
X242	emphcic	If yes, para-cicatricial?	Yes ☐ (1)	No ☐ (2)
X243	lynod	Lymphnode enlargement?	Yes ☐ (1)	No ☐ (2)
X244	lynodist	If yes, what is the distribution? (mark all)	Right hilar ☐ (1) Left hilar ☐ (2)	Mediastinal ☐ (3)
X245	lynocalc	If yes, is there lymphnode calcification?	Yes ☐ (1)	No ☐ (2)
X246	medmass	Mediastinal mass?	Yes ☐ (1)	No ☐ (2)
X247	pleff	Pleural effusion?	Yes ☐ (1)	No ☐ (2)
X248	pleffdist	If yes, distribution	Uniliateral ☐ (1)	Bilateral ☐ (2)
X249	plthick	Pleural thickening?	Yes ☐ (1)	No ☐ (2)
X250	plthickdist	If yes, distribution	Unilateral ☐ (1)	Bilateral ☐ (2)
X251	plthickloc	If yes, location	Apical ☐ (1)	Basal ☐ (2)
X252	plplaq	Pleural plaques?	Yes ☐ (1)	No ☐ (2)
X253	pneumo	Pneumothorax?	Yes ☐ (1)	No ☐ (2)
X254	cardeff	Pericardial effusion?	Yes ☐ (1)	No ☐ (2)
X255	cardmeg	Cardiomegaly?	Yes ☐ (1)	No ☐ (2)
X256	pad	Pulmonary Artery dilatation?	Yes ☐ (1)	No ☐ (2)
X257	bones	Bones and chest wall abnormal?	Yes ☐ (1)	No ☐ (2)
X258	soft	Soft tissues (neck, axillae, abdomen) abnormal?	Yes ☐ (1)	No ☐ (2)

10.2.4 CT Thorax: diagnostic



15327

Form RROC_X2c CT Thorax report: consensus TB - RROC study

Study ID ☐☐☐☐☐☐ **Date** ☐☐ ☐☐☐ ☐☐☐☐ (D D M O N Y Y Y Y)

Diagnosis

X2c03	chronic	Chronic lung disease	Yes ☐ (1)	No ☐ (2)
X2c04	chronicdx	If yes, which diagnoses (mark all)	Bronchiectasis ☐ (1)	Pulmonary fibrosis (not TB related) ☐ (5)
			Scarring ☐ (2)	Unspecified ILD ☐ (6)
			Destroyed lung ☐ (3)	Suspected PAH ☐ (7)
			COPD/emphysema ☐ (4)	Other ☐ (8)
X2c05	scar	If scarring, details	Post-TB ☐ (1)	Non-specific ☐ (2)
X2c06	destroy	If destroyed lung, what extent?		1-25% ☐ (1)
				26-50% ☐ (2)
				51-75% ☐ (3)
				76-100% ☐ (4)
X2c07	chroniccom	Comments on chronic lung disease		
X2c08	acute	Acute lung disease?	Yes ☐ (1)	No ☐ (2)
X2c09	acutedx	If yes, which diagnoses? (mark all)	Lobar pneumonia ☐ (1)	Pleural effusion ☐ (4)
			Multifocal pneumonia ☐ (2)	Miliary TB ☐ (5)
			Atypical pneumonia ☐ (3)	Other ☐ (6)
X2c10	activetb	Compatible with active TB?	Yes ☐ (1)	No ☐ (2)
X2c11	activecom	Comments on actue lung disease		
X2c12	othercom	Other comments		

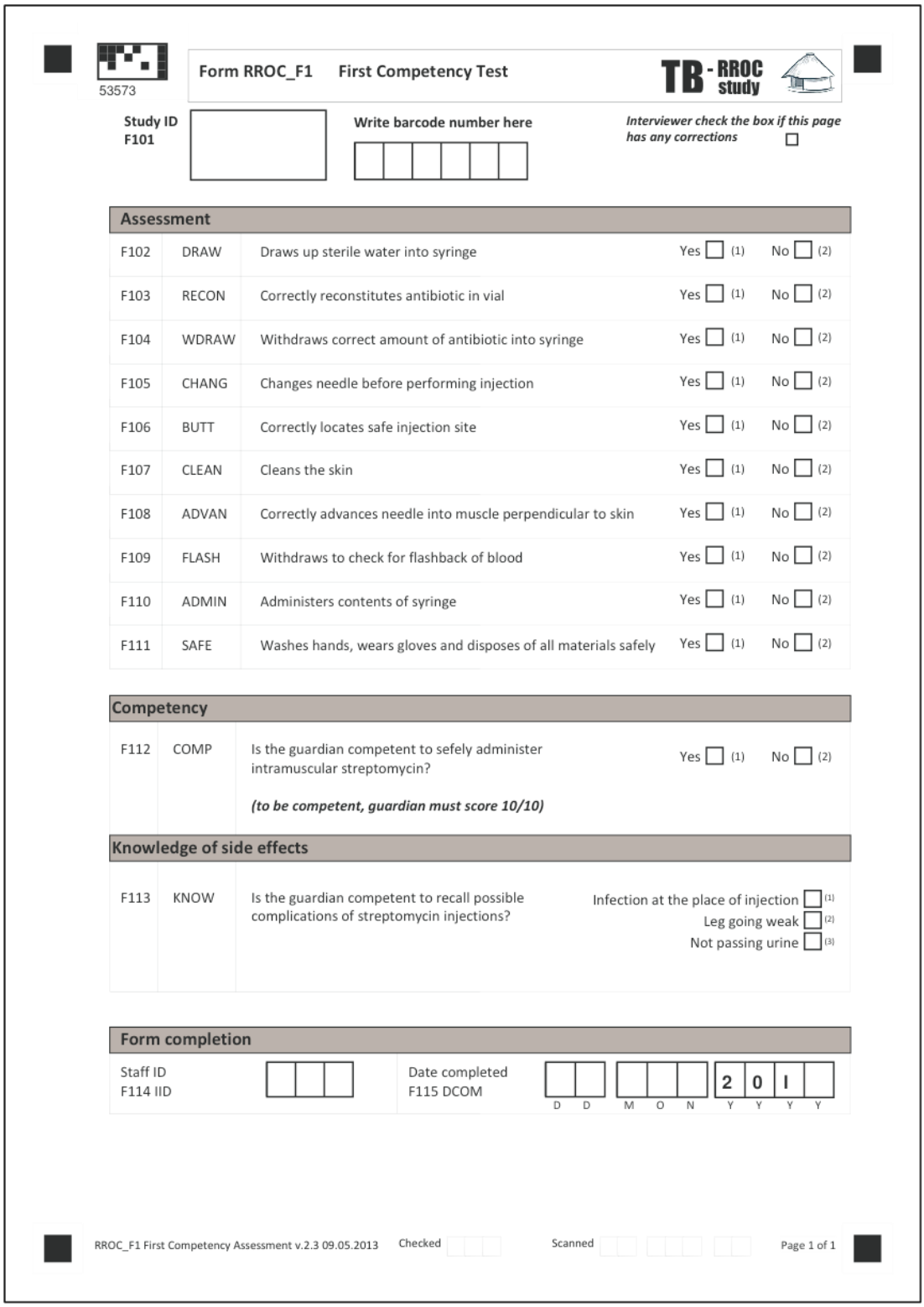
Form completion

Staff ID X2c13 IID ☐☐☐

Date completed X2c14 DCOM ☐☐ ☐☐☐ 2 0 I ☐ (D D M O N Y Y Y Y)

RROC_X2c CT Thorax report consensus v1.1 03.09.2014 Checked ☐☐ Scanned ☐☐ ☐☐☐☐ ☐☐ Page 1 of 1

10.3 Competency assessment form



53573

Form RROC_F1 First Competency Test

TB - RROC study

Study ID F101

Write barcode number here

Interviewer check the box if this page has any corrections ☐

Assessment

F102	DRAW	Draws up sterile water into syringe	Yes ☐ (1)	No ☐ (2)
F103	RECON	Correctly reconstitutes antibiotic in vial	Yes ☐ (1)	No ☐ (2)
F104	WDRAW	Withdraws correct amount of antibiotic into syringe	Yes ☐ (1)	No ☐ (2)
F105	CHANG	Changes needle before performing injection	Yes ☐ (1)	No ☐ (2)
F106	BUTT	Correctly locates safe injection site	Yes ☐ (1)	No ☐ (2)
F107	CLEAN	Cleans the skin	Yes ☐ (1)	No ☐ (2)
F108	ADVAN	Correctly advances needle into muscle perpendicular to skin	Yes ☐ (1)	No ☐ (2)
F109	FLASH	Withdraws to check for flashback of blood	Yes ☐ (1)	No ☐ (2)
F110	ADMIN	Administers contents of syringe	Yes ☐ (1)	No ☐ (2)
F111	SAFE	Washes hands, wears gloves and disposes of all materials safely	Yes ☐ (1)	No ☐ (2)

Competency

F112	COMP	Is the guardian competent to sefely administer intramuscular streptomycin? ***(to be competent, guardian must score 10/10)***	Yes ☐ (1) No ☐ (2)

Knowledge of side effects

F113	KNOW	Is the guardian competent to recall possible complications of streptomycin injections?	Infection at the place of injection ☐ (1) Leg going weak ☐ (2) Not passing urine ☐ (3)

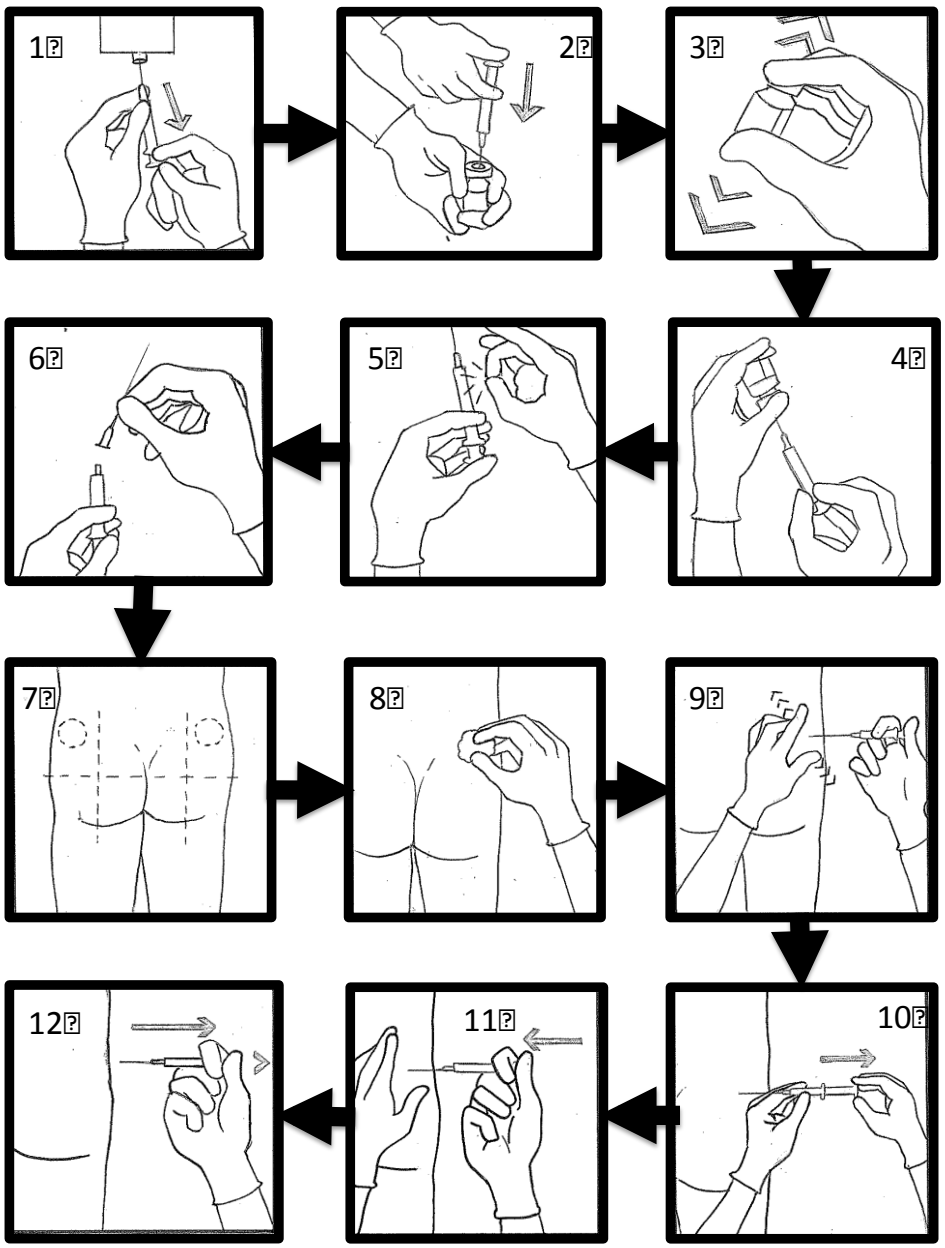
Form completion

Staff ID F114 IID ☐☐☐

Date completed F115 DCOM ☐☐ ☐☐☐ 2 0 I ☐ (D D M O N Y Y Y Y)

RROC_F1 First Competency Assessment v.2.3 09.05.2013 Checked ☐☐☐ Scanned ☐☐ ☐☐☐ ☐☐ Page 1 of 1

10.4 Instruction card



Back of instruction card:

Kumbukirani:

Kusamba mmanja, musanabaye ndi mukamaliza kupeleka Jakisoni.

Kuvala ma gulovesi nthawi zonse pamene mukupeleka jakisoni.

Kutaya masingano ndi masilinji mu bokosi la chikasu, pamene mwamalizira kugwiritsa ntchito.

Kupeleka Jakisoni kwa odwala ***tsiku liri lonse***

Musapeleke jakisoni kwa wina aliyense kupatula odwala yekha.

Woyang'anira odwala yekhayo amene waphunzitsidwa, ndi amene ayenera kupeleka jakisoni.

Ngati pangakhale zovuta:
Lolemba kufikira Lachisanu 8 koloko mpaka 5 koloko, phone:

Helen Mangochi: 0998654382
Jimmy Chavula: 0998654383
George Musowa: 0998654384

Nthawi ina ili yonse:
Pitani ku Ngozi kapena ku Wodi 3A ku chipatala cha Queen Elizabeth central Hospital.

Back of instruction card in English:

TB - RROC Study

Remember to:

Wash your hands before and after giving the injection.

Wear gloves at all times when giving the injection.

Throw away all needles and syringes into the yellow box when you have finished using them.

Give the injection to the patient ***every day***.

Do not give the injection to anybody else apart from the patient.

Only the trained guardian should give the injection.

In case of problems:
Monday – Friday 8am – 5pm phone:

Helen Mangochi: 0998654382
Jimmy Chavula: 0998654383
George Musowa: 0998654384

All other times:
Attend AETC or ward 3A at
Queen Elizabeth central Hospital.

10.5 Home monitoring form

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

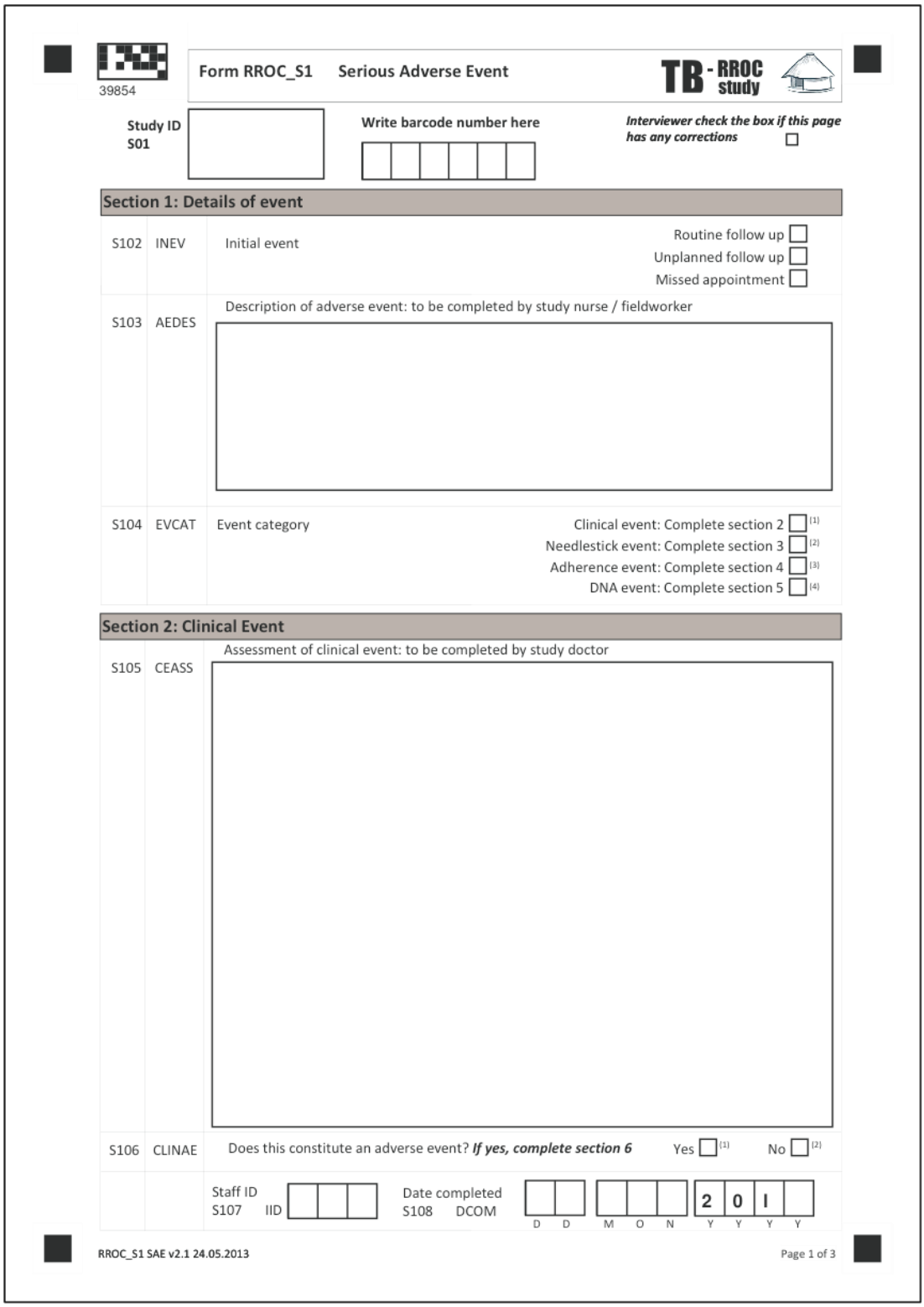
Ulendo	Tsiku	Date	Nthawi
1			
2			
3			
4			

Ngati pangakhale zovuta:

Lolemba kufikira Lachisanu 8 koloko mpaka 5 koloko, phone:
Helen Mangochi: 0998654382
Khondwani Mzembe: 0998654383
George Musowa: 0998654384

Nthawi ina ili yonse:
Pitani ku Ngozi kapena ku Wodi 3A ku chipatala cha
Queen Elizabeth central Hospital.

10.6 Adverse Event form



39854

Form RROC_S1 Serious Adverse Event

TB - RROC study

Study ID S01

Write barcode number here

Interviewer check the box if this page has any corrections ☐

Section 1: Details of event

S102	INEV	Initial event	Routine follow up ☐ Unplanned follow up ☐ Missed appointment ☐
S103	AEDES	Description of adverse event: to be completed by study nurse / fieldworker	
S104	EVCAT	Event category	Clinical event: Complete section 2 ☐ (1) Needlestick event: Complete section 3 ☐ (2) Adherence event: Complete section 4 ☐ (3) DNA event: Complete section 5 ☐ (4)

Section 2: Clinical Event

S105	CEASS	Assessment of clinical event: to be completed by study doctor	
S106	CLINAE	Does this constitute an adverse event? ***If yes, complete section 6***	Yes ☐ (1) No ☐ (2)

Staff ID S107 IID ☐☐☐

Date completed S108 DCOM ☐☐ ☐☐☐ 2 0 1 ☐ (D D M O N Y Y Y Y)

RROC_S1 SAE v2.1 24.05.2013

Page 1 of 3

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Form RROC_S2 Serious Adverse Event — TB - RROC study

Study ID S209 ☐☐☐☐☐☐

Interviewer check the box if this page has any corrections ☐

Section 3: Needle-stick event

S210	DEXP	Date of exposure	☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)
S211	TEXP	Time of exposure (use 24 hour clock)	☐☐ : ☐☐
S212	DASEXP	Date of assessment by clinician	☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)
S213	TASEXP	Time of assessment by clinician	☐☐ : ☐☐
S214	PEPAE	PEP prescribed? ***If yes, complete section 6***	Yes ☐ (1) No ☐ (2)
		Staff ID S215 IID ☐☐☐	Date completed S216 DCOM ☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)

Section 4: Adherence event

S217	DADH1	Date of the first adherence problem	☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)
S218	ADH1	Number of missed doses at first adherence event	☐☐
S219	DADH2	Date of the second adherence assessment	☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)
		Second adherence assessment	
S220	ADLAST	*Number of days since last visit*	☐☐
S221	AMISS	How many injections have you missed since the last visit?	☐☐
S222	AVLEFT	*Number of vials left at last visit*	☐☐
S223	AVREM	*Number of vials remaining*	☐☐
S224	AVUSE	*Number of vials used*	☐☐
S225	AVCOU	*Missed doses by vial count* ***(If >1 missed dose since last vist, readmit to ward)***	☐☐
S226	ADHAE	Was the patient readmitted to the ward? ***If yes, complete section 6*** Yes ☐ (1) No ☐ (2)	
		Staff ID S227 IID ☐☐☐	Date completed S228 DCOM ☐☐ (D D) ☐☐☐ (M O N) 2 0 I ☐ (Y Y Y Y)

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Form RROC_S 3 Serious Adverse Event

TB - RROC study

Study ID S 329 ☐☐☐☐☐☐

Interviewer check the box if this page has any corrections ☐

Section 5: Missed appointment

S 330	DDNA	What date was the missed appointment?	D D M O N 2 0 I Y Y Y Y
S 331	PHPT	Was the patient telephoned?	Yes ☐ (1) No ☐ (2)
S 332	PHG	Was the guardian telephoned?	Yes ☐ (1) No ☐ (2)
S 333	PHALTNO1	Was the first alternative contact telephoned?	Yes ☐ (1) No ☐ (2)
S 334	PHALTNO1	Was the second alternative contact telephoned?	Yes ☐ (1) No ☐ (2)
S 335	VISIT	Was a visit made to the home of the patient?	Yes ☐ (1) No ☐ (2)
S 336	LTFAE	Loss to follow up event identified?	Yes ☐ (1) No ☐ (2)
		Staff ID S 337 ☐☐☐ Date completed S 338 dcom	D D M O N 2 0 I Y Y Y Y

Section 6: SAE Classification: *To be completed by study doctor at the end of the event*

S 339	SAE	SAE confirmed?	Adverse Event ☐ (1) Serious Adverse Event ☐ (2) Unexpected Serious Adverse Event ☐ (3) No Adverse Event ☐ (4)
S 340	SAECLAS	PRIMARY classification of adverse event (Mark one response)	Death ☐ (1) LIfe threatening illness ☐ (2) Hospitalisation ☐ (3) Persistent or significant disability or incapacity ☐ (4) Loss to follow up ☐ (5) BBV exposure ☐ (6) Not applicable ☐ (7)
S 341	SAEHOSP	PRIMARY reason for hospitalisation, illness or death (Mark one response)	Illness related to TB ☐ (1) Illness not related to TB ☐ (2) Change in urine output - renal failure confirmed ☐ (3) Change in urine output - no renal failure ☐ (4) Unable to give injections at home - safety problem ☐ (5) Unable to give injections at home - adherence problem ☐ (6) Infection at injection site ☐ (7) Hepatitis ☐ (8) Rash ☐ (9) Other ☐ (10) Not applicable ☐ (11)
S 342	SAEDIS	Cause of possible permanent disability	Sciatic nerve palsy ☐ (1) Deafness ☐ (2) Other ☐ (3) Not applicable ☐ (4)

Form completion

Staff ID S 343 IID ☐☐☐ Date completed S 344 DCOM D D M O N 2 0 I Y Y Y Y

Date initial DSMB notification _ _/_ _/_ _ Date final DSMB notification _ _/_ _/_ _

10.7 TB-RROC DSMB

10.7.1 TB-RROC DSMB Terms of Reference

The DSMB reports to the trial sponsor, the research ethics committees, the PI and TSG.

The DSMB are an advisory group, they do not have the power or the authority to stop a trial or change a protocol. The DSMC report their findings to the sponsor, the relevant IRB(s) and TSG who make the decision whether to continue, suspend, modify or stop a trial or amend the protocol.

The DSMB has access to data for the trial so that they can see any emerging risks such as frequency or severity in adverse events.

Their monitoring should also include considering external factors to the study such as therapeutic or scientific developments that may have an impact on the safety of participants or the ethics of the study.

Confidentiality is paramount. The DSMB must protect the confidentiality of the trial data and the results of monitoring.

Their role and responsibilities are:

- To review the research protocol and the plans therein for data and safety monitoring;
- To review any proposed modifications to the study prior to their implementation;
- To review serious adverse events and adverse event reports provided by the PI at monthly intervals;
- To review the planned interim analysis of study data after recruitment of 130 patients, as outlined in the protocol;
- To inform the Sponsor, Research Ethics Committee and Site Investigators on the acceptability of continued recruitment to the Trial. If the DSMB makes a recommendation that a trial should be stopped or suspended, the sponsor will take the necessary action to ensure that new recruitment to the trial is stopped whilst the DSMB's report is evaluated and the research ethics committee is informed. If there is disagreement between the DSMB and the trial steering group and/or the research ethics committee on a recommendation to stop or suspend a trial, the sponsor may convene an independent external advisory committee to arbitrate. During any such process, recruitment of new participants to the trial will be suspended;
- To consider any requests for the release of interim trial data and to recommend to the Trial Steering Group on the advisability of this;
- To consider any issues or concerns raised by local investigators, funding bodies etc that the Trial Steering Group has not been able to resolve;
- To review and approve primary trial abstracts and manuscripts to give an assurance that the results are fairly presented and that the conclusions are appropriate.

10.7.2 TB-RROC DSMB interim report

TB-RROC study DSMB meeting 12th September

1. The meeting took place in the Wellcome Trust Tropical Centre seminar room. Professor Stephen Gordon, Dr Mas Chaponda, Professor Neil French (chair), Dr Danielle Cohen (investigator), Professor Bertie Squire (investigator) were present. Dr Cohen provided an overview of the trial to date. Key areas discussed were
    a. Errors in counting recruits into each arm explained and corrected
    b. Lower than expected number of end-points with 7 deaths and one treatment default.
    c. Review of case histories of all deaths in the two arms: 5 in community group, 2 in hospital group.
2. The DSMB commended the investigators on the conduct of the study to date.
3. The DSMB recommend the continuation of the study.
4. The lower than expected end-points are the principal threat to the study and under current end-point accumulation there is a risk that the study may be underpowered to provide a conclusive result. Consequently the DSMB recommend
    a. Review with the other investigators whether additional analytical methods could be applied to the data
    b. Consider whether it is feasible to extend recruitment to increase end-point ascertainment.
5. The DSMB has no formal plan to meet prior to the termination of the study unless requested by the investigators. We will continue to monitor monthly mortality data.

10.8 Qualitative topic guides

10.8.1 Patient interviews

Thank you for agreeing to talk to me. I am interested in learning about what it's been like getting treatment for TB. I will be recording the interview, just so that I can make sure I have an accurate record of our conversation. If you feel uncomfortable at any time we can stop, and if we are talking about something you don't want to talk about just tell me and we can skip it.

- What does the participant know about TB

- What are the participant's experiences of TB treatment
    - Describe your treatment to me.
    - Tell me about your injections.
    - What is it like being in hospital.
    - What is it like getting treatment at home.
    - What is it like being in your community when you are taking TB treatment.
    - How do you feel about having TB treatment.
    - Did you feel differently about TB at the beginning of your treatment compared to now. Tell me more about that.

- I would like to hear more about the healthcare workers you met during treatment. Can you tell me about them
    - How often did you have contact with healthcare workers.
    - What role did they play in your treatment.

- How, if at all, has having TB treatment affected your life.
    - Work
    - Relationships – spouse, children, friends
    - Financial situation

- What things influence people to continue taking TB treatment.
    - What things help somebody to take TB treatment.
    - What things make it difficult for somebody to take TB treatment.
    - What things would make it easier for you to take TB treatment.

- Do you talk to anyone about your TB treatment.
    - Who do you talk to.
    - Tell me what it's like talking to other people about TB

- What do you think will happen to your health in the future.

- Those are the main topics I had planned to cover, but is there anything else you would like to tell me about? Is there something we have missed that you think I should know?

10.8.2 Guardian interviews

Thank you for agreeing to talk to me. I am interested in learning about what it's been like being a guardian for a patient being treated for TB. I will be recording the interview, just so that I can make sure I have an accurate record of our conversation. If you feel uncomfortable at any time we can stop, and if we are talking about something you don't want to talk about just tell me and we can skip it.

- Can you tell me what you know about TB.

- Tell me about your experiences of being a guardian for a patient with TB
  - Describe the treatment to me.
  - Tell me about the injections your patient received.
  - Tell me about learning to do the injections.
  - What is it like being in hospital.
  - What is it like looking after your patient at home.
  - Describe what your community thinks about people who are on TB treatment
  - Tell me about your position in the community since you started giving injections to your patient
  - Did you feel differently about TB at the beginning of your patient's treatment compared to now. Tell me more about that.

- I would like to hear more about the healthcare workers you met during your patient's treatment. Can you tell me about them
  - How often did you have contact with healthcare workers.
  - What role did they play in the treatment of your patient.
  - What were the interactions you had with healthcare workers as a guardian.

- How, if at all, has being a guardian for a TB patient affected your life.
  - Work
  - Relationships – spouse, children, friends
  - Financial situation

- What influences people to continue taking TB treatment.
  - What things help somebody to take TB treatment.
  - What things make it difficult for people to take TB treatment.
  - What things do you think would make it easier for people to take TB treatment.

- Do you talk to anyone about TB.
  - Who do you talk to.
  - Tell me what it's like talking to other people about TB

- Those are the main topics I had planned to cover, but is there anything else you would like to tell me about. Is there something we have missed that you think I should know.

10.8.3 Focus Group Discussions

Tell me what you know about TB?

- Transmission / causes
- Diagnosis
- Treatment (formal & informal)

How, if at all, does TB affect your community?

- Individual people
- Households
- Socially
- Economically
- Adults & children

Why do you think some people are given TB treatment at home and others have to be in hospital?

How, if at all, does being in hospital for TB treatment affect people?

What do you think about people taking TB treatment in the community?

Have you heard about people who get injections as part of TB treatment?

- Tell me what you have heard about
- What do you think about injections for TB?

(If they have heard about CMB but they have the wrong idea about what it involves, probe further e.g. where did they hear about it? What have they been told?)

Some people with TB are in hospital because they need to have injections every day for TB, but many of them are well enough to be at home. There is an idea that guardians can be trained by the nurses in the hospital to give injections to their patients. This would mean that if patients were well enough, they could go home. What do you think of that?

- Patient
- Guardian
- Household
- Friends
- Wider community
- Health care service (responsibility of community v health care workers)

- How would you feel if you had a TB patient and the hospital offered to teach you to give injections to your patient, so that you could give them treatment at home?

10.8.4 Key informant interviews

- Role of the Key Informant in TB care
- Views of inpatient care for TB patients
    - Possible problems & advantages for patients
    - Possible problems & advantages for guardians/friends/relatives
    - Possible problems & advantages for Health care systems
- Opinions about the intervention
    - Effects for patients
    - Effects for guardians/friends/relatives
    - Effects for communities
    - Effects for health care systems
- General view of the intervention

10.8.5 Hospital observations

- Setting and environment of the hospital – male & female wards, nursing station, TB office
- General condition of the patients – physical and psychological
- Behaviours of patients on the ward
- Relationships between patients – interactions, discussions
- Behaviours of guardians – on and around the ward
- Interactions between patients and guardians
- Relationships between patients, guardians and healthcare workers
- The process of injection administration on the ward

10.8.6 Community observations

- Setting and environment of the household
- General condition of the patient – physical and psychological
- Interaction between patient and guardian
- Interaction between patient and the rest of the household/community
- Interaction between guardian and the rest of the household/community
- The process of the guardian administering the injection
- Reaction of the patient, guardian, household members, wider community to the fieldworker


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