Center for Innovative Drug Development &

Therapeutic Trials for Africa (CDT-Africa)

College of Health Sciences

Addis Ababa University

SURVIVAL OF PATIENTS WITH TUBERCULOSIS IN RETREATMENT PROGRAMME WITH GUARDIAN ADMINISTERED STREPTOMYCIN IN MALAWI

BY

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Thesis submitted to Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa in partial fulfilment for the award of Master of Science in Clinical Trials.

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DECLARATION

I declare that this thesis is my own work and has not been submitted to any institution for a degree qualification.

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Fides Mboma Date

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ACRONYMS

ADR	Adverse Drug Reactions
ART	Antiretroviral therapy
CD4	Cluster of Differentiation 4
CDT	Center for Innovative Drug Development and Therapeutic Trials
CI	Confidence Interval
COMREC	College of Medicine Research Ethics Committee
CONSORT	Consolidated Standards of Reporting Trials
CRFs	Case Report Forms
DOT	Directly Observed Treatment
DST	Drug Susceptibility Testing
EPTB	Extra pulmonary tuberculosis
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Interquartile Range
ITT	Intention To Treat
KM	Kaplan Meier
MLW	Malawi Liverpool Wellcome Trust
MDR-TB	Multi Drug Resistant Tuberculosis
MoH	Ministry of Health
MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
NGO	Non-Governmental Organisation
OPAT	Outpatient Parenteral Antibiotic Therapy
PTB	Pulmonary tuberculosis
RAD	Retreatment After Default

RCTs	Randomized Controlled Trials
TB	Tuberculosis
WHO	World Health Organisation

ABSTRACT

Background: Current ambulatory approaches for delivering treatment to patients with tuberculosis in Malawi have significant operational delivery challenges. This led to a clinical trial aimed at establishing if guardian administered streptomycin is non-inferior to hospital administered streptomycin. In order to establish effectiveness of guardian administered streptomycin, all integral outcomes including survival need to be assessed.

Objectives: Based on secondary analysis of existing trial dataset, this study aimed to compare survival of patients with tuberculosis who received streptomycin administered at hospital or at home by a guardian controlling for potential factors that may confound or mediate effect of the treatments.

Methods: In the original study - a non-inferiority, parallel, randomised, open label, phase III trial –204 patients were randomized to receive streptomycin at the hospital or in their homes where it was administered by a patient nominated guardian. One hundred and one patients were randomized into hospital arm while 103 into home-based group. Patients were followed up for ten months. In this study, comparison of survival between the treatment delivery options employed Logrank test. Cox proportional hazard model was used to identify factors that confound or mediate survival of patients. Potential factors included age, sex, TB class, TB category, HIV status, smoking status, drinking status and employment status of participants and education level of household head.

Results: No significant difference was observed in survival of patients between the two groups (p-value = 0.726, HR 1.15 (0.52 to 2.55). All covariates except unemployment had no effect on survival of patients (CI for HR had 1).

Conclusion: Use of patient nominated trained lay carers to administer streptomycin provides a potential convenient and cost-effective approach for treating patients with recurrent and drug resistant TB. However, decision for its adoption should be cautious due to small sample size

used, switching of critically ill patients from home-based group to hospital arm, inadequate information on how patients selected guardians and lack of details on how TB resistance was assessed. A follow up study on assessment of acceptability of the proposed model of care would help understand if it could be successfully adopted and used to deliver long term TB injectable agents to patients.

CHAPTER ONE

1.1 Background

Tuberculosis (TB) is one of the top ten causes of death worldwide (1). In 2017, an estimate of ten million people worldwide acquired TB infection resulting to approximately 1.6 million deaths (1,2). Ninety percent of all reported cases were of age fifteen years and above, and the ratio of male to female was two to one (1). If not treated, a person with pulmonary TB may infect an average of 10-20 people within a year (2). In Malawi, TB continues to be a public health problem which affects the productive age group (1,2). It is also the leading cause of death among people living with Human Immunodeficiency Virus (HIV) (3). In 2017, Malawi had an incidence of 133 new cases per 100 000 (1). This has increased the burden on health care delivery and has greatly affected the socio-economic development of the country (2).

World Health Organization (WHO) recommends that standard treatment for TB whether drug-susceptible or drug-resistant should be given as ambulatory care (4). This is because once an effective treatment regimen has commenced, the bacteriological load is rapidly reduced and the patient becomes non-infectious within a few days (4). Patients receive treatment while in their community as long as they have no complications that may require medical attention (4). The ambulatory approach for treating patients with tuberculosis gives community members a chance to provide social support services to the patients. Such services have been consistently reported as important factors that affect key health outcomes including survival of the patients (5). In Malawi, patients with tuberculosis are required to either travel daily from their homes to a health facility or be visited by professional health worker who would provide them with the TB treatment (6). These methods have significant operational delivery challenges (6).

Programmes of outpatient parenteral antibiotic therapy (OPAT) have been successfully established in developed countries (6). Evidence shows that the services are safe, well received by users and highly cost effective (6). In developing countries, patients with diabetes mellitus are prescribed insulin and they successfully administer sub-cutaneous injections at home (6). However, little is known about carer-administered intramuscular treatment in resource constrained settings (6). In view of this, a clinical trial was conducted in Malawi to assess if guardian administered intramuscular streptomycin for retreating patients with tuberculosis is non-inferior to streptomycin administered at the hospital (6). The trial was conducted when category II regimen (2SRHE/1RHZE/5RHE) was the recommended regimen for retreating patients with tuberculosis for countries with low prevalence of Multi Drug Resistant (MDR)-TB and with no access to drug susceptibility testing (DST) (7).

Non-inferiority trials aim to demonstrate that the intervention is not less effective than the standard treatment by more than the tolerable amount (8). The primary objective of the trial was to assess treatment success at the end of two-month intervention period. Treatment success was defined as still alive and on treatment having completed 2 months streptomycin injection (6). WHO recommends assessment of all integral outcomes including survival in establishing effectiveness of drug treatment and its mode of administration (7). Survival analysis helps in estimating patients' prognosis and in assessing viability of the available treatment options. The study on guardian administered streptomycin did not assess survival of the patients.

Also, several studies on survival of patients with TB have been conducted. Most of the studies' population was treated at the hospital or health facility. In Sub-Saharan Africa, no studies have been conducted on survival of patients with tuberculosis retreated with guardian administered streptomycin. Therefore, this study compared time to death of patients with tuberculosis

retreated with guardian administered streptomycin and those retreated at the hospital with same regimen.

1.2 Problem statement

Patients with TB are exposed to unsuccessful treatment and adverse drug reactions (ADRs) once retreated with streptomycin in absence of drug susceptibility testing results (7). Nevertheless, WHO guidelines still recommends use of streptomycin for retreating patients who either defaulted or had a relapse in cases where DST results are not routinely available (7). Continuous prescription of streptomycin may be associated with other unacceptable outcomes including death. However, little is known about its effect on survival of patients with tuberculosis.

Several studies on survival of patients with TB have been conducted. In these studies, the population of interest was either all patients with tuberculosis or patients with multidrug resistant (MDR)-TB or patients co-infected with TB-HIV (9–21). Most of the studies' population was treated at the hospital or health facility. In Sub-Saharan Africa, no studies have been conducted on survival of patients with tuberculosis retreated with guardian administered streptomycin.

In order to determine effectiveness of drug treatment, assessment of all outcomes including survival must be done (1). Survival analysis helps in estimating patients' prognosis and practicality of using the available treatment options. The trial on guardian administered streptomycin did not assess survival of the patients. This may have biased the conclusion about its effectiveness. In addition, assessing clinical response also helps medical practitioners determine if the regimen will be effective in treating the patients. In order to build on the trial

findings, this project assessed survival and clinical response of the patients retreated with category II regimen.

1.3 Rationale for the study

Despite evidence that streptomycin is associated with unsuccessful treatment, ADRs and acquisition of TB drug resistance, total phase out of the regimen depends on availability of molecular drug susceptibility testing (7). Therefore, understanding survival and clinical response of patients with tuberculosis following initiation of category II regimen will build on the available evidence about its effectiveness. Such evidence will further help medical practitioners, policy makers and other health stakeholders in deciding on the use of streptomycin when DST results are not available.

As the use of Xpert MTB/RIF expands, more patients will be diagnosed and enrolled on MDR-TB treatment (7). Long term injectable agents including streptomycin are prescribed for patients with MDR-TB (3). Having treatment provided using a decentralised model of care such as guardian administered, is a practical approach to scale up treatment and care for patients eligible for long term injectable agents. Therefore, comparing survival of patients with tuberculosis retreated with guardian administered streptomycin with those retreated with similar injections at the hospital, will add on the existing evidence about its effectiveness. This may enhance the acceptability of using guardians in administering the injections. Establishing that guardian administered streptomycin works the same as hospital administered streptomycin, may provide a convenient and cost-effective approach for retreating patients with tuberculosis and other diseases that require long term treatment. This may further contribute towards achieving one of the End TB strategy that aims to ensure that none of the affected families endures catastrophic costs by the year 2025 (22).

1.4 Objectives

1.4.1 General objective

To assess survival and clinical response in terms of sputum smear results at the end of two month treatment intervention of patients with tuberculosis retreated with streptomycin while controlling for potential factors that may confound or mediate the effect of the treatment.

1.4.2 Specific objectives

i. To compare survival of patients with tuberculosis retreated with guardian administered streptomycin with those who received streptomycin at the hospital.
ii. To identify factors associated with survival of patients with tuberculosis retreated with guardian administered intramuscular streptomycin.
iii. To compare clinical response in terms of sputum smear results at the end of 2 months of treatment intervention of patients with tuberculosis retreated with guardian administered streptomycin with those who received streptomycin at the hospital.

1.5 Research questions

i. Is there any difference on the survival of patients retreated with guardian administered streptomycin and those who received streptomycin at the hospital?
ii. What factors are associated with survival of patients with tuberculosis retreated with guardian administered intramuscular streptomycin?
iii. Is there any difference on the clinical response s in terms of sputum smear results at the end of month two of treatment intervention of patients with tuberculosis retreated with guardian administered streptomycin and those who received streptomycin at the hospital?

1.6 Hypothesis

The survival probability of patients with tuberculosis retreated with guardian administered streptomycin is not worse than that of patients who received streptomycin at the hospital.

CHAPTER TWO

Literature review

2.1 Overview of the review

The review is divided into two sections. The first section presents a summary of research articles considered for review while the second part gives synthesized results from the included articles. Studies on TB related survival and on effectiveness of home or community-based care for treating patients with tuberculosis were considered. The review gathered diverse information from the articles to guide the methodology and understand the potential contribution and implication of this study. The gathered information includes type of patient with tuberculosis considered in various studies, sample size used, the study designs employed, statistical methods for data analysis and results of the studies.

2.2 Summary of information from the articles considered for review

Table 1- Summary of study methods and results of articles considered for review

Author & year of publication	Study title	Study objective	Sample size	Study population	Design	Setting	Analysis	Summary of Results
Horter et al., 2014 (23)	Qualitative analysis of a patient-centred model of care for MDR-TB patients	To examine experiences of patients and key stakeholders of home-based MDR-TB care	30	MDR-TB patients, family members, village health team members, health care workers & key informants from MoH & NGOs	Qualitative study	Kitgum & Lamwo districts, Uganda	Grounded theory	Homebased care was acceptable to patients, families, communities & health care workers. Was perceived as safe, conducive for recovery, facilitating psychosocial support & allowing more free time & earning potential for patients & caretakers.
Cohen et al., 2018 (24)	Qualitative evaluation of hospital vs community-based management of patients on TB injectable treatments	To examine experiences of people receiving injections as part of TB treatment delivered in hospital and community-based settings	35	TB retreated patients, guardians and key informants	Qualitative study	Hospitals and communities in Malawi	Thematic content	Patients and guardians benefitted from better environment, social interactions & financial stability. Concerns about potential for patients' health or relationships to be adversely affected in the community

Loveday et al., 2015 (25)	Community-based care vs. centralised hospitalisation for MDR-TB patients in South Africa	To determine most effective care of model between community-based and central specialised hospital	1549	MDR-TB	Non-randomised observational prospective cohort (2008-2010)	Community and hospital in South Africa	Logistic regression, Cox's proportional hazards model	MDR-TB patients were more likely to have a successful treatment outcome if they were treated at a community-based site (adjusted OR 1.43, P = 0.01). Home-based care more effective than hospital based (higher cure, lower default, earlier treatment initiation and increased treatment success).
Mhimbira et al., 2016 (26)	Home-Based and Facility-Based DOT therapy of TB treatment in Tanzania	To compare TB treatment outcomes in home-based and facility-based DOT of TB patients	4835	Adult TB patients	Retrospective cohort	Temeke district and Dar es Salaam in Tanzania	Logistic regression	TB patients under home-based care had higher mortality than patients under facility based.
Birlie et al., 2015 (13)	Time to death and risk factors amongst TB patients in Ethiopia	To assess time to death and associated risk factors among TB patients	769	All TB patients	Retrospective cohort (2012-2016)	Clinic & hospital in Ethiopia	KM, Logrank, Generalized Wilcoxon, Tarone-W, Cox proportional	Median survival: 10 days Mean survival: 25.8 days Predictors of mortality: type of TB, ART status, and use of Cotrimoxazole prophylaxis therapy

Amante TD & Ahemed TA, 2014 (12)	Risk factors for unsuccessful (failure, default, death) TB treatment in Ethiopia	To identify risk factors for unsuccessful TB treatment outcome in Ethiopia	976	All TB patients	Case referent study	TB clinics in Ethiopia	Logistic regression	Lack of contact person, smear negative treatment category, smear positive sputum test at 2nd month after initiation of treatment & HIV positive status
Aung et al., 2019 (11)	Survival rate and mortality risk factors among TB-HIV co-infected patients.	To examine survival rate and risk factors for mortality among TB-HIV co-infected patients	3598	TB-HIV co-infected patients registered from	Retrospective study (2005-2016)	ART center in Japan	Kaplan Meier & Cox proportional hazard model	Survival rate of 82% at 5 years & 58.1% at 10 years. Mortality risk factors: Bedridden, low baseline CD4 count & being second line ART regimen
Getahun et al., 2011 (20)	Mortality and associated risk factors in TB patients treated under DOT programme.	To determine magnitude and identify risk factors associated with time to death among TB patients treated under DOTS programme	6430	All TB patients	Retrospective cohort (2004-2009)	Health centres in Ethiopia	Kaplan-Meier, Step-wise Cox's regression model	Mortality rate: 3.7% Mean & median survival time: 7.2 months & 7.9 months resp. Predictors of time to death: treatment center, patient category and body weight

Dizaji et al., 2018 (19)	Risk factors associated with survival of PTB in Iran	To determine risk factors associated with survival of TB patients	5313	Adults newly diagnosed with PTB	Retrospective cohort (2005-2015)	Hospitals	Generalised gamma regression model	Death rate: 33.4% Risk factors: Age, sex, smoking status, education level, HIV status, Diabetes mellitus & comorbidities
Medicina F, 2012 (21)	The poor survival among PTB patients in Mexico	To analyse survival in patients with PTB and factors associated with such survival	305	Adults diagnosed with PTB	Longitudinal prospective study	hospitals	Kaplan Meier, log-rank test and Cox regression	Risk factors: Age, treatment duration
Senbeta et al., 2014 (9)	Survival analysis & associated risk factors in TB patients	To determine survival rate and risk factors associated with TB	202	All TB cases	Prospective cohort	Hospitals and health centres, in Ethiopia	Kaplan Meier and Cox proportional model	Survival rate: 94.1% Survival risk factors: Place of treatment and income level
Adamu et al., 2017 (27)	High mortality among TB patients on treatment in Nigeria	To assess time to mortality after treatment onset	1424	All TB cases	Retrospective cohort (2010-2014)	TB treatment centre.	Kaplan Meier and Cox proportional model	Death rate: 16.6% (3.68 per 100 pm) Risk factors: HIV status, previous TB treatment, and type of TB
Pardeshi G, 2009 (18)	Survival analysis and risk factors for death in TB patients on DOT in India	To describe the survival pattern of patients on short course DOT	716	TB patients registered for DOT	Retrospective cohort	TB unit	Kaplan Meier, Log-rank test and Cox regression	Survival rate: > 90% Risk factor for death: age

Zhang et al., 2018 (28)	Treatment outcomes of MDR treatment in China	To examine treatment outcomes and factors associated with poor outcome of MDR in China	820	MDR-TB patients	Prospective observational cohort (2009-2013)	Hospital	Cox proportional	Death rate: 6.7% Risk factors: Old age, patients type (relapse and failure), cavitary disease
Ayakaka et al., 2015 (29)	High mortality associated with retreatment of TB patients in Uganda	To determine long-term outcome under programmatic conditions of patients who were prescribed the retreatment regimen	1826	MDR-TB	Retrospective Study (1997-2003)	National TB and leprosy registry in Uganda	KM, Cox regression	Death rate: 62% Risk factors: Having < 2 treatment courses and not completing retreatment
Ayakaka et al., (30)	Effectiveness of category II for TB patients in Uganda	To determine effectiveness of this retreatment regimen	288	Smear positive pulmonary TB	Prospective Cohort Study	Hospital in Uganda	Logistic regression, Kaplan Meir, Cox proportional	Unsuccessful treatment outcome: 20% & 26% of HIV-uninfected and HIV-infected patients respectively Predictors of mortality: history of failure, poor adherence, age, lower karnofsky score, low baseline CD4, not initiating ART
Rocha et la., 2018	Effect of inpatient and outpatient	To identify factors associated with	6986	New cases and cases with	Noncurrent Cohort study with passive	Health centers	Proportional hazard	Age above 60, admission to hospital with emergency services, HIV associated TB

	care on TB treatment outcome in Ethiopia	deaths in subjects diagnosed with TB.		previous treatment	follow up (2006-2008)			
Fantaw et al., 2018 (31)	Assessment of survival status & risk factors for mortality among MDR-TB patients in Ethiopia	To assess survival status & risk factors for mortality of MDR-TB patients	164	MDR-TB patients	A retrospective cohort Study (2013-2017)	Hospital	Kaplan Meir, Cox proportional	Median survival time: 400.5 days Survival status at 24 months: 72% Mortality risk factors: HIV, low initial body weight, age and co-morbidities

2.3 Synthesis of the review

Several studies have been conducted on comparative effectiveness between home-based treatment and clinic-based treatment. Ambulatory care for MDR-TB was effective as it was found to be safe, conducive for recovery and with high treatment success rates (23,25,32). The patients also benefited from the psychosocial support as facilitated by the caregivers who were able to continue with their personal undertakings (23). This approach was acceptable and preferred by patients, families, communities, and health care workers (23). Home-based care was also found to be more cost-effective than hospital-based care for TB patients (33). However, treatment administered by trained lay providers or healthcare workers was recommended over that administered by family members or unsupervised treatment (32). A study on guardian administered streptomycin found that patients and guardians benefited from better environment, social interactions and financial stability (24). However, concerns were raised about the potential for patients' health or relationship to be adversely affected in the community (24). Evidence shows that TB patients on home based DOT were more likely to die than patients on facility based DOT (26).

TB related studies have reported varying results on survival of patients with the median survival ranging from 10 days to 7.9 months (13,20,31). The population of interest was either MDR-TB patients or all TB patients or TB-HIV co-infected patients. Contextual factors and period of study may have also contributed to the difference in the observed survival. Different survival rates have also been reported with measurements taken at different time points (9,11,18,31). For instance, 72% of MDR-TB patients survived at 24 months of treatment initiation while approximately 90% of TB patients survived at the end of intensive phase of DOT TB treatment (18). A survival rate of more than 90% was as a result of early diagnosis and the start of appropriate treatment (9).

Mortality rate of TB patients was diverse in various countries, for TB patient type, and for specific period of assessment (19,20,27–29,34). Uganda reported the highest death rate of 62% among TB patients retreated for TB (29). This was attributed to having less than or equal to two treatment courses and not completing retreatment (29). However, death rate was as low as 3.7% (20). Predictors of death were different in various studies. These include type of TB, HIV status, ART status, baseline CD4 count, patient category, age, sex, smoking status, alcohol consumption, education level, diabetes mellitus, and income level. Patients with extra-pulmonary TB (EPTB) or with both EPTB and pulmonary TB were at higher risk of dying (13,27). Survival was lower in TB patients who were smokers, old, had diabetes mellitus, with HIV infection, with low baseline CD4 count, and alcohol drinkers (11,12,17–19,21,27,28,31,35,36). Retreated patients were more likely to die than newly diagnosed TB patients (20,28). Illiterate cases had the highest rate of death and the ratio of male patients in TB death cases was significantly higher than female cases (19). TB patients with high socio-economic status were more likely to die than those with middle and low income (9). It was also established that most death occurred soon after treatment onset (9,27).

CHAPTER THREE

Methodology

3.1 Trial design

This study was a secondary analysis of dataset for a non-inferiority, parallel, randomised, open label, phase III trial on delivery of long-term injectable agents for tuberculosis by lay carers. The primary objective of the original trial was to assess treatment success at the end of two-month intervention period. Treatment success was defined as still alive and on treatment having completed 2 months streptomycin injection (6). This study, compared survival of the patients from the two treatment delivery options at the end of TB retreatment programme. It also assessed clinical response in terms of sputum smear results after completion of 2 months' streptomycin injection.

3.2 Participants

The parent trial was conducted in Malawi. Patients reporting for TB retreatment at Queen Elizabeth Central Hospital in Blantyre and Bwaila Hospital in Lilongwe, were enrolled between June, 2013 and August, 2015. Patients were eligible if they were 16 years or older, able to provide informed consent, fit for discharge and identified a suitable guardian who administered injections safely and passed the competency assessment. Patients were excluded from the trial if they were identified as having MDR-TB or Rifampicin resistant TB or pregnant or not planning to stay in the area for the duration of the intervention. Patients admitted to hospital to start retreatment were identified by reviewing the TB and ward registers. Diagnosis of TB was based on clinician assessment in usual operational conditions.

3.3 Sample size determination

The original study assumed that 87% of patients receiving standard of care would be alive and on treatment at the end of the 60-day intervention period. The sample size was calculated based on a non-inferiority margin of 6%. Using a one-sided alpha at a level of 0.05, in order to achieve a power of 80%, a sample size of 268 was required. This study was constrained to use the sample size presented in the dataset. However, a non-inferiority margin of 6% is large for mortality. At the same time, it is difficult to specify a non-inferiority margin for death because it is ethically difficult to determine number of acceptable deaths (38). Also, it is unethical to use large sample sizes in trials whose outcome is irreversible because patients may be potentially exposed to inferior care (39).

3.4 Interventions

Participants in the parent trial were randomised either into the hospital (standard treatment) or into home-based care group (intervention group). Participants remained on the ward until randomisation. Randomisation took place during the intensive phase of tuberculosis retreatment. Participants randomised into intervention group received home-based care from guardians who were trained to deliver intramuscular streptomycin. Patients were asked to nominate a guardian for training. In Malawi, guardians are usually family members or friends who accompany patients, and perform a variety of tasks including basic care and assisting with medications (37). Once the guardian was able to perform injections safely, they underwent a structured competency assessment. Participants randomised to receive standard care were admitted to hospital for 60-days to get daily streptomycin injections. However, all patients presenting with clinical adverse events were reviewed by a study clinician regardless of their treatment arm.

3.5 Variables and outcomes for the project

The primary outcome of this project was survival of patients with tuberculosis retreated with category II regimen in home and hospital setting followed up for ten months. The secondary outcome was patients' clinical response to the regimen in terms of sputum smear test results at the end of two month of treatment intervention. The independent variables considered were age (in years), sex (male, female), smoking status (smokers, non-smokers), HIV status (positive, negative), alcohol consumption (never, 1-4 times a month, > 1 time a week), TB class (pulmonary, extra pulmonary), TB patient category (relapse, fail, RAD, EPTB, smear negative), education level of household head (none, Primary, Secondary and University), and employment status (employed, unemployed and casual work).

3.6 Data management

3.6.1 Data collection, entry, cleaning and other quality control issues

Data for the original trial was collected using paper case record form and was doubly entered into Microsoft Access database. The two databases were compared, discrepancies were checked against the source document and updates made to the databases to produce a validated batch of the entered data. Data was stored on a secured SQL server. Data cleaning was performed by the study statistician before database lock. Locked database was transferred to Stata software for analysis.

3.6.2 Data quality assessment and diagnosis

Data quality assessment was performed by checking values outside the expected normal range, misspecifications, missing values, and errors or inconsistencies in date recordings. This was achieved through frequency distributions, cross tabulations, and manual checks. Any errors or inconsistencies were corrected through logical reasoning or imputation method. Appendix 3 has a summary of data quality assessment and diagnosis done in this study.

3.7 Statistical analysis

The analysis for this project was performed using Stata version 14.2. Skewed data was summarised using the median and interquartile ranges (IQRs). Categorical data was summarised using frequencies and percentages. All tests of significance were performed at a significance level of 0.05. Treatment outcomes at eighth month were classified as cured, completed, failed, defaulted, died and transferred out. All patients with an outcome other than death were considered to have survived upon completion of the eight-month treatment therapy. The time that a patient was alive was determined by calculating the differences in days from start of treatment until the day when the patient died. Kaplan Meir survival curve was used to estimate survival of TB patients retreated with streptomycin. Logrank test was used to assess the difference in survival of patients with TB retreated at the hospital and those who received guardian administered intramuscular streptomycin. Univariate and multivariable analysis of the effect of predictors on survival was conducted using the Cox proportional hazard model. Univariate analysis helped identify significant factors with an effect on survival. All independent variables were entered in one step when building the Cox Proportional hazard model for multivariable analysis. The model was used to describe the association and quantify the effect of the covariates in presence of other variables on death rate of patients with TB. A hazard ratio of greater than one indicated a positive effect. The covariate with no effect on survival of the patients had its 95% confidence interval for the hazard ratio containing a null value of 1. Schoenfeld residual test were performed to assess the assumption of constant hazard ratio for patients retreated at the hospital and those retreated at home. Fisher's exact test was used to assess if there was any difference in the clinical response between the two groups.

3.8 Ethical consideration

The original study was approved by the College of Medicine Research Ethics Committee (COMREC). The COMREC number is P.020/13/1340. A copy of the ethical approval letter for the trial that was obtained from COMREC is attached as appendix 1.

3.9 Dissemination plan

The project report will be submitted to Addis Ababa University and will be uploaded in the University website. The findings will also be submitted for consideration to be published in a reputable journal. Study results will also be disseminated in relevant health related conferences conducted at national and international level.

CHAPTER FOUR

Results

4.1 Study participants

A total of 456 patients were assessed for eligibility within the period June, 2013 to February, 2015. This study analysed 204 patients who were randomised to receive TB retreatment at the hospital or at home. One hundred and one patients were randomised into the hospital arm while 103 patients into home-based group. Two hundred and fifty-two patients were excluded as they were not randomized to either of the two groups (Figure 1). The patients were not randomised as some declined to participate in the trial, guardian declined, were pregnant, had MDR-TB, were not staying in the area where the trial was conducted, patient died, transferred out or were unfit to be enrolled in the trial.

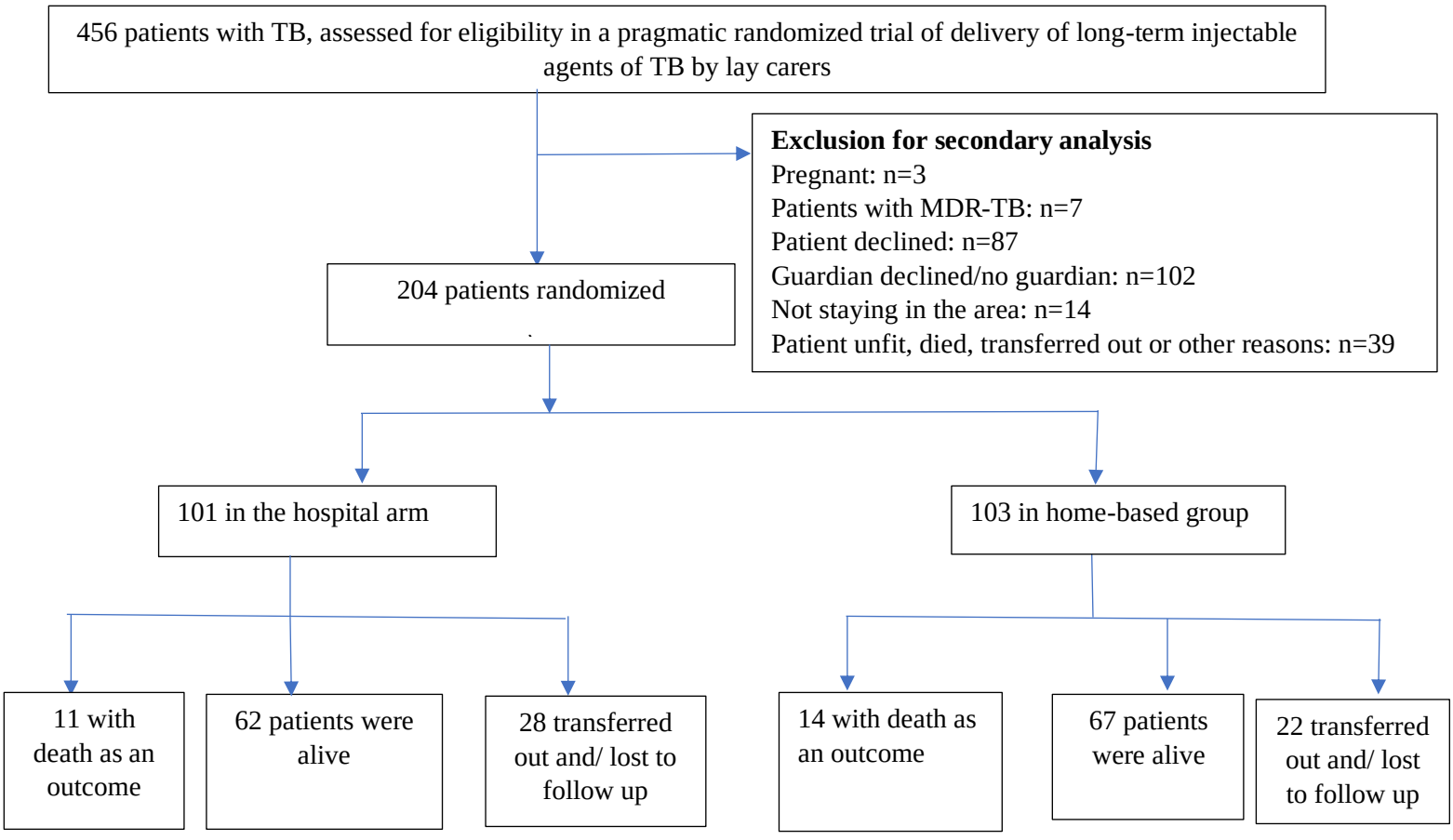


Figure 1- CONSORT diagram for secondary analysis of the pragmatic trial dataset on delivery of long-term TB injectable agents by lay carers.

4.2 Demographic and clinical characteristics of participants

Table 2- Demographic and clinical characteristics by total study population, group by randomisation and outcome category

		Group by randomisation		Outcome category		
Participant characteristics	**Total study population n=204**	**Home based n=103**	**Hospital based n=101**	**Died n=25**	**Alive n=129**	**Transferred out &/ lost to follow up n=50**
Age						
Median & IQR	36.5(30-44)	36 (30-43)	37 (30-44)	37 (32-43)	37 (31-44)	34.5 (30-42)
Sex						
Male	142 (69.6%)	77 (74.8%)	65 (64.4%)	15 (60.0%)	85 (65.9%)	42 (84.0%)
Female	62 (30.4%)	26 (25.2%)	36 (35.6%)	10 (40.0%)	44 (34.1%)	8 (16.0%)
Education level of household head						
None	12 (5.9%)	4 (3.9%)	8 (7.9%)	1 (4.0%)	7 (5.4%)	4 (8.0%)
Primary	88 (43.1%)	42 (40.8%)	46 (45.5%)	9 (36.0%)	22 (45.0%)	21 (42.0%)
Secondary	84 (41.2%)	43 (41.8%)	41 (40.6%)	13 (52.0%)	36 (38.0%)	22 (44.0%)
University	20 (9.8%)	14 (13.6%)	6 (5.9%)	2 (8.0%)	22 (11.6%)	3 (6.0%)
Employment status	129 (63.2%)	63 (61.2%)	66 (65.4%)	12 (48.0%)	85 (65.9%)	32 (64.0%)
Employed	67 (32.8%)	36 (35.0%)	31 (30.7%)	12 (48.0%)	41 (31.8%)	14 (28.0%)
Unemployed	8 (3.9%)	4 (3.9%)	4 (4.0%)	1 (4.0%)	3 (2.3%)	4 (8.0%)
Casual work(ganyu)						
Smoking status						
Non smokers	141 (69.1%)	68 (66.0%)	73 (72.3%)	20 (80.0%)	92 (71.3%)	29 (58.0%)
Smokers	63 (30.9%)	35 (34.0%)	28 (27.3%)	5 (20.0%)	37 (28.7%)	21 (42.0%)
Drinking status						
Never	145 (71.1%)	69 (67.0%)	76 (75.3%)	19 (76.0%)	94 (72.9%)	32 (64.0%)
1-4 times a month	19 (9.3%)	10 (9.7%)	9 (8.9%)	2 (8.0%)	9 (7.0%)	8 (16%)
>1 a week	40 (19.6%)	24 (23.3%)	16 (15.8%)	4 (16.0%)	26 (20.1%)	10 (20%)
TB class						
Pulmonary	182 (89.2%)	98 (95.2%)	84 (83.2%)	21 (84.0%)	115 (89.2%)	46 (92.0%)
Extra-pulmonary	22 (10.8%)	5 (4.9%)	17 (16.8%)	4 (16.0%)	14 (10.9%)	4 (8.0%)
TB category						
Relapse	117 (57.4%)	63 (61.2%)	54 (53.5%)	13 (52.0%)	78 (60.5%)	26 (52.0%)
RAD	9 (4.4%)	4 (3.9%)	5 (5.0%)	1 (4.0%)	4 (3.1%)	4 (8.0%)
Fail	15 (7.4%)	10 (9.7%)	5 (5.0%)	0 (0.0%)	13 (10.1%)	2 (4.0%)
Other	63 (30.9%)	26 (25.2%)	37 (36.7%)	11 (44.0%)	34 (26.4%)	18 (36.0%)
HIV status						
Positive	158 (77.5%)	73 (70.9%)	85 (84.2%)	23 (92.0%)	95 (73.6%)	40 (80.0%)
Negative	46 (22.6%)	30 (29.1%)	16 (15.8%)	2 (8.0%)	34 (26.4%)	10 (20.0%)

Table 2 gives summary of the demographic and clinical characteristics of participants by total study population, group by randomisation and outcome category. The median age of the participants was 36.5 years (IQR 30-44 years). Participants who received hospital-based treatment comparatively were slightly older (37 years with IQR 30-44 years) than those who received treatment at home (36 years with IQR 30-43 years). Participants who died had comparable same median age as those who were alive (37 years with IQR 32-43 years and 31-44 years respectively). Participants who were transferred out or lost to follow up were slightly younger compared to those who died and were alive (34.5 years with IQR 30-42 years).

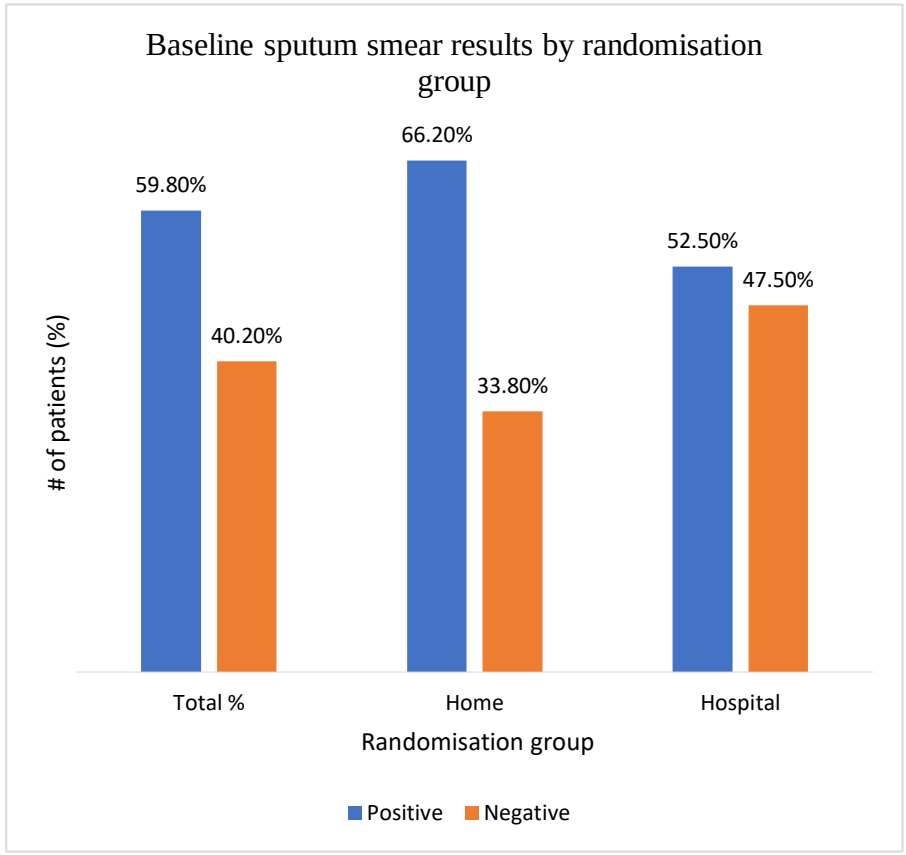
Most participants were male 142 (69.6%), HIV positive 158 (77.5%), non-smokers 141 (69.1%), and with no history of drinking alcohol 145 (71.1%). The participants suffered most from pulmonary TB 182 (89.2%), which was classified most commonly as relapse 117 (57.4%). A total of 129 (63.2%) participants were employed. Most household heads either had primary [88 (43.1%)] or secondary education [84 (41.2%)]. Similar traits are also observed within each randomised group (Table 3).

At the end of the TB treatment, a total of 129 (66.2%) participants were alive, 25 (12.3%) had died, and 50 (21.6%) were either transferred out or lost to follow up. Among the 129 participants who were alive, 62 were from the hospital arm while 67 were from the home-based group (Table 3). Out of the 25 deaths, 11 occurred in the hospital while 14 happened at home (Table 3).

Table 3- Detailed demographic and clinical characteristics of the participants in each group by outcome category.

	Home based group*			Hospital based group*		
Participant characteristics	**Died n=14**	**Alive n=67**	**Transferred out &/lost to follow up n=22**	**Died n=11**	**Alive n=62**	**Transferred out &/lost to follow up n=28**
Age						
Median & IQR	37 (35-44)	35 (30-43)	36.5 (32-42)	35 (24-43)	38.5 (33-45)	34 (27-44)
Sex						
Male	9 (64.3%)	49 (73.1%)	19 (86.4%)	6 (54.6%)	36 (58.1%)	23 (82.1%)
Female	5 (35.7%)	18 (26.9%)	3 (13.6%)	5 (45.4%)	26 (41.9%)	5 (17.9%)
Education level of household head						
None	0 (0.0%)	4 (6.0%)	0 (0.0%)	1 (9.1%)	3 (4.8%)	4 (14.3%)
Primary	6 (42.9%)	26 (38.8%)	10 (45.5%)	3 (27.3%)	32 (16.1%)	11 (39.3%)
Secondary	7 (50.0%)	26 (38.8%)	10 (45.5%)	6 (54.6%)	23 (35.5%)	12 (42.9%)
University	1 (7.1%)	11 (16.4%)	2 (9.0%)	1 (9.1%)	4 (14.5%)	1 (3.6%)
Employment status						
Employed	8 (57.1%)	38 (56.7%)	17 (77.3%)	4 (36.4%)	47 (75.8%)	15 (53.6%)
Unemployed	5 (35.7%)	15 (22.4%)	4 (18.2%)	7 (63.6%)	15 (24.2%)	9 (32.1%)
Casual work	1 (7.1%)	3 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)
Smoking status						
Non-smokers	10 (71.4%)	45 (67.2%)	13 (59.1%)	10 (90.9%)	47 (75.8%)	16 (57.1%)
Smokers	4 (28.6%)	22 (32.8%)	9 (40.9%)	1 (9.1%)	15 (24.2%)	12 (42.9%)
Drinking status						
Never	10 (71.4%)	45 (67.2%)	14 (63.6%)	9 (81.8%)	49 (79.0%)	18 (64.3%)
1-5 times a month	0 (0.0%)	6 (9.0%)	4 (18.2%)	2 (18.2%)	3 (4.8%)	4 (14.3%)
>1 a week	4 (28.6%)	16 (23.9%)	4 (18.2%)	0 (0.0%)	10 (16.1%)	6 (21.4%)
TB class						
Pulmonary	12 (85.7%)	64 (95.5%)	22 (100%)	9 (81.8%)	51 (82.3%)	24 (85.7%)
Extra-pulmonary	2 (14.3%)	3 (4.5%)	0 (0.0%)	2 (18.2%)	11 (17.7%)	4 (14.3%)
TB category						
Relapse	6 (42.9%)	44 (65.7%)	13 (59.1%)	7 (63.6%)	34(54.8%)	13 (46.4%)
RAD	1 (7.1%)	2 (3.0%)	1 (4.6%)	0 (0.0%)	2 (3.2%)	3 (10.7%)
Fail	0 (0.0%)	10 (14.9%)	0 (0.0%)	0 (0.0%)	3 (4.8%)	2 (7.1%)
Other	7 (50%)	11 (16.4%)	8 (36.4%)	4 (36.4%)	23 (37.1%)	10 (35.7%)
HIV status						
Positive	14 (100%)	42 (62.7%)	17 (77.3%)	9 (81.8%)	53 (85.5%)	23 (82.1%)
Negative	0 (0.0%)	25 (37.3%)	5 (22.7%)	2 (18.2%)	9 (14.5%)	5 (17.9%)

* The difference in number of deaths between the two groups was not statistically significant (2-sided Fisher's Exact p=0.828)



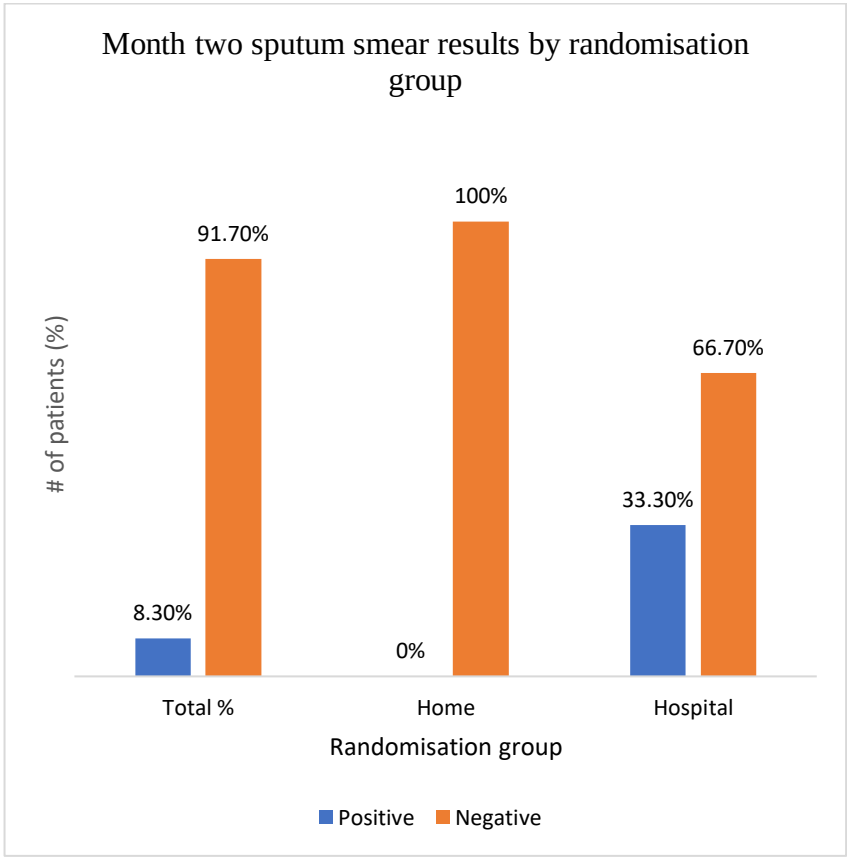


Figure 2- Sputum smear results at baseline and at month two

One hundred and thirty-two participants (71 under home care management and 61 under hospital care management) were tested for sputum smear at the start of TB treatment (Figure 2). Out of these, 79 (59.8%) tested positive while 53 (40.2%) tested negative. Overall, 47 (66.20%) participants under home-based treatment and 32 (52.46%) under hospital treatment, tested positive at baseline. Only 12 (9 from home and 3 from hospital) participants had sputum smear results at month two. Sputum smear results for all the 9 (100%) participants under home care management were negative at month two. On the other hand, two (66.67%) participants treated at the hospital had negative sputum smear results at month two. Results of Fisher's exact test indicate no significant difference in clinical response of participants in terms of sputum smear results at month two (p-value = 0.250, risk difference = -0.82 (-1.05 to 0.59)) Risk ratio could not be estimated.

4.3 Estimation

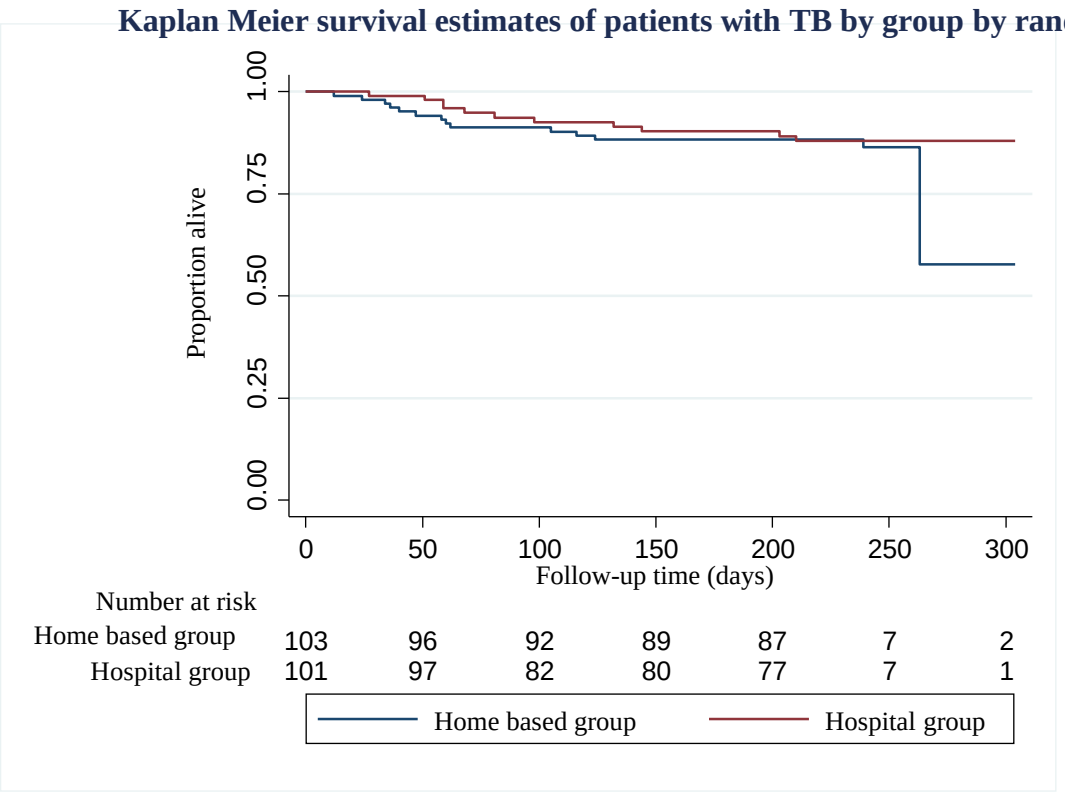


Figure 3- KM survival estimates of participants with TB based on group by randomisations

Figure 3 shows estimates of survival probabilities for the participants who were followed up for ten months (300 days). The survival probabilities in the two groups were almost the same for the period starting from initiation of TB treatment until 260 days. However, the proportion of participants surviving beyond 260 days dropped from approximately 85% to 55% in the home-based group. However, results of the Logrank test indicate no significant difference in survival of the participants between the two groups (P-value =0.726, HR 1.15 (0.52 to 2.55)).

4.4 Test of proportional hazard assumptions

Table 4- Test of proportional hazards assumptions for both covariates specific and global

Characteristic	**category**	**p-value**
Randomisation group	Hospital*	
	Community	0.255
Age	NA	0.832
Sex	Male*	
	Female	0.284
Education level of household head	None*	
	Primary	0.236
	Secondary	0.616
	University	0.463
Employment status	Employed*	
	Unemployed	0.406
	Casual work(ganyu)	0.638
Smoking status	Never*	
	Ever	0.379
Drinking status	Never*	
	1-4 times a month	0.310
	>1 time a week	0.503
TB class	Pulmonary*	
	Extra-pulmonary	0.412
TB category	Relapse*	
	RAD	0.673
	Fail	1.000
	Other	0.852
HIV status	Positive*	
	Negative	0.682
Global test	NA	0.942

*Reference group

The results in table 4 show no evidence of the violation of the proportional-hazards assumption (p-value>0.05). Therefore, the proportion of the hazard rates for all the variables considered in this analysis were constant at each specific time point.

4.5 Outcomes for univariate and multivariable analysis of predictors on survival of patients

Table 5- Univariate and multivariable intention to treat analysis of time to death using cox regression model

Characteristic	**Categories**	**p-value**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Randomisation group	Hospital* Community	 0.726	 1.15 (0.52-2.55)	 1.56 (0.66-3.71)
Age	NA	0.787	1.00 (0.96-1.03)	0.97 (0.93-1.02)
Sex	Male* Female	 0.272	 1.57 (0.70-3.49)	 0.89 (0.30-2.67)
Education level of household head	None* Primary Secondary University	 0.925 0.533 0.995	 1.10 (0.14-8.79) 1.91 (0.25-14.60) 1.01 (0.09-11.25)	 1.40 (0.16-12.07) 2.82 (0.32-24.50) 1.66 (0.13-21.80)
Employment status	Employed* Unemployed Casual work	 0.014 0.618	 2.86 (1.24-6.60) 1.68 (0.22-13.05)	 3.33 (1.23-9.01) 3.00 (0.28-32.48)
Smoking status	Never* Ever	 0.305	 0.60 (0.22-1.60)	 0.54 (0.16-1.85)
Drinking status	Never* 1-4 times a month >1 a week	 0.843 0.559	 0.86 (0.20-3.71) 0.72 (0.24-2.15)	 0.62 (0.12-3.20) 1.02 (0.28-3.65)
TB class	Pulmonary* Extra-pulmonary	 0.271	 1.83 (0.62-5.36)	 1.00 (0.29-3.49)
TB category	Relapse* RAD Fail Other	 0.839 1.000 0.152	 1.24 (0.16-9.51) NA 1.82 (0.80-4.12)	 1.31 (0.14-12.02) NA 1.46 (0.54-3.92)
HIV status	Positive* Negative	 0.093	 0.29 (0.07-1.23)	 0.30 (0.06-1.39)

* Reference group

Note-The sample size included for each analysis was 204.

About 15% of the patients treated within their homes by lay carers were more likely to die compared to those treated at the hospital (HR = 1.15). However, this was not statistically significant (P-value = 0.726 and CI (0.52-2.55)). Place of treatment also had no effect on survival of the patients when the factors age, sex, TB class, TB category, HIV status, smoking status, drinking status and employment status of the participants and education level of household head were kept constant (adjusted CI (0.66-3.71)).

A one-year increase in age had no effect on survival of the patients (HR = 1.00). This too was statistically non-significant (P-value = 0.787 and CI (0.96-1.03)). Relatively more female patients were likely to die than male patients (HR = 1.57) although this again was not statistically significant (P-value = 0.272 and CI (0.70-3.49)). Keeping other factors constant, both age and sex showed no effect on survival of the patients (adjusted CI for age (0.93-1.02) and adjusted CI for sex (0.30-2.67)).

About 90% of the patients from families whose household head had secondary education were more likely to die than those whose household head had no education (HR = 1.91). However, this was not statistically significant (P-value = 0.533 and CI (0.25-14.60)). Patients whose household head had primary education were 10% more likely to die than those whose household head had no education (HR = 1.10). These results were also statistically non-significant (P-value =0.925 and CI (0.14-8.79)). The probability of surviving was almost the same for patients whose household head had university education and those with no education (HR = 1.02). However, this effect was also statistically non-significant (P-value = 0.09-11.25 and CI (0.09-11.25)). Education level of household head had no effect on survival of the patients when all factors were kept constant (adjusted CI for all categories of education level of household head include the null value of 1).

Unemployed patients were almost three times more likely to die than employed patients (HR = 2.86). The effect of unemployment on survival of the patients was statistically significant (P-value = 0.014 and CI (1.24-6.60)). About 70% of the patients involved in casual work were more likely to die than employed patients (HR = 1.68). However, the effect was not statistically significant (P-value = 0.618 and CI (0.22-13.05)). Similar observations for the categories of employment status were noted when all other characteristics were kept constant using the multivariable cox proportional hazard model (adjusted CI for unemployed group (1.23-9.01) and adjusted CI for casual workers (0.28-32.48)).

In comparison to patients who had never smoked before, 40% of the patients who had ever smoked were more likely to survive (HR = 0.60). Nevertheless, the results were not statistically significant (P-value = 0.305 and CI (0.22-1.60). The likelihood of dying was about 15% lower in patients drinking 1-4 bottles a month and about 30% lower in patients drinking more than once in a week compared to patients who were non-drinkers (HR = 0.86 and 0.72 respectively). But the results were not statistically significant (drinking 1-4 bottles in a month, P-value = 0.843 and CI (0.20-3.71); drinking more than once in a week, P-value = 0.559 with CI (0.24-2.15)). A multivariable cox proportional hazard model also shows that smoking status and drinking status had no effect on survival of the patients (Ever smoked, adjusted CI (0.16-1.85); Drinking 1-4 times a month, adjusted CI (0.12-3.20); Drinking more than once a week, adjusted CI (0.28-3.65)).

More patients with extra-pulmonary TB were likely to die than patients with pulmonary TB (HR = 1.83). Compared to patients with relapse, none of the patients whose TB treatment Failed were likely to die (HR = 0.00). Additionally, 24% with RAD as a TB treatment outcome and 82% of the patients with TB treatment outcomes other than RAD or Fail were more likely to

die than those whose treatment outcome was a relapse (HR for RAD = 1.24 and HR for Other = 1.82). It should be pointed out that TB class and all the TB categories were statistically non-significant including when other factors were kept constant (TB Class, P-value = 0.271, crude CI (0.62-5.36) and adjusted CI (0.62-5.36); Fail, P-value = 1 with no CI for both univariate and multivariable model; RAD, P-value = 0.839, crude CI (0.16-9.51) and adjusted CI (0.14-12.02); Other, P-value = 0.152, crude CI (0.80-4.12) and adjusted CI (0.54-3.92)).

Almost 70% of the patients who were HIV negative, were more likely to survive than patients who were HIV positive (HR = 0.29). This too was statistically non-significant (P-value = 0.093 and crude CI (0.07-1.23)). Likewise, HIV status had no effect on survival of the patients when all other covariates were kept constant (adjusted CI (0.06-1.39)).

CHAPTER FIVE

5.1 Discussion

The ambulatory approaches for administering TB treatment currently in use in Malawi face operational delivery challenges. Therefore, research on novel approaches that can overcome such challenges is essential in understanding about their effectiveness. Survival is one of the important factors to be considered when assessing effectiveness of such approaches. Also, assessing clinical response helps medical practitioners determine if the regimen will be effective in treating the patients.

This study demonstrated no significant difference in survival as well as in clinical response of patients who received treatment at home with the help of guardians and those under hospital care management. Clinical response was measured in terms of sputum smear results. Guardians were trained in the technique of intramuscular injection, including injection procedure, sterile technique and disposal of sharps. The results agree with what was found in the original trial. No significant difference was observed in successful treatment (alive and on treatment) at the end of intensive phase between the two treatment arms (6).

Overall, this study has established that age, sex, TB class, TB category, HIV status, smoking status and drinking status of participants, as well as education level of household head had no significant effect on survival of the patients. However, literature reported that such factors had an effect on survival of the patients (11,12,17–19,21,27,28,31,35,36). It should be noted though that predictors of death varied from one study to another. This study further showed that employment status had an effect on survival of the patients. Unemployed patients were at a higher risk of dying compared to employed patients. Unemployment may imply that the patients

were living below the poverty lines. Studies identified poverty as a key factor contributing to higher mortality (9).

Though not statistically significant, results of this study show high likelihood of survival for smokers and alcohol drinkers. This goes against what is known as such factors are significantly associated with TB mortality (40,41). This might be the case since almost all patients [62 (98%)] considered to be smokers were previous smokers. In line with this, literature indicates that the risk of dying due to TB is reduced in people who stopped smoking and becomes almost similar to non-smokers as time progresses (40). As for alcohol drinking, greater exposure to it puts the patients at higher risk of dying (41). Therefore, further analysis of the amount of alcohol that they was consumed by the patients versus the risk of dying could help understand the findings observed in this study. However, this was not done as such factors were already found to be non-significant.

Study design, contextual factors, period of study and sample size may have contributed to the observed differences in the effects of the covariates with those from previous studies. Almost all studies considered for review were non-randomised with the population of interest being either patients with MDR-TB or all patients with TB or patients co-infected with TB-HIV. This study used data from a randomised trial in which participants had equal chance of being allocated to the hospital or home group. Randomisation ensured that patients in each group had similar distribution of the mentioned characteristics. Participants in this study were patients with TB in need of retreatment and without MDR or rifampicin resistant.

Follow up period for this study was less than one year while the follow up period in other studies ranged from two to eleven years. Longer follow up periods in previous studies together with the types of study design used ensured inclusion of more participants in the studies with their outcomes captured at the end of the study. On the contrary, this study used smaller sample size with a good number of participants being lost to follow up. This might have had an effect on the findings of the study as the analysis might have been underpowered to detect the true difference in survival between the two groups. This also applies to the assessment of clinical response between the two treatment arms. Data for this study was collected at only two hospitals of the urban areas of Malawi. This poses as a one of the limitations as the findings on survival cannot be generalised to other contexts.

In spite of the results demonstrating non-significant difference in survival of the patients under home based care management and those under hospital care management, implication for clinical relevance need to be carefully thought of. Besides the use of small sample size that might have made the study not to be powered enough to detect significant difference, all patients presenting with clinical adverse events were reviewed by a study clinician. This was done regardless of the patients' treatment arm. This implies that patients in the home-based group still received some care from the hospital staff hence biasing the results. Additionally, critically ill patients from home-based group were transferred to the hospital arm. This means that selection bias that is avoided through randomisation was not completely eliminated from the study. Moreover, use of the Intention to Treat (ITT) approach for data analysis might have had biased the outcome for this study.

Regardless of the fact that guardians were nominated by patients, little is known about how patients arrived at the decision of nominating guardian of their choice. This might have had an impact on delivery of care to the patients, hence affecting the outcome for this study. Also, the original trial did not indicate how TB resistance was assessed. Understanding how such an assessment was done is critical in establishing eligibility of the participants involved in the study. Considering the nature of this trial, blinding of the participants and medical staff was impossible as it was obvious the treatment arm to which patients belonged. This might have introduced possible bias in patient management and influenced decisions to withdraw patients especially from the home-based care group. Hence, the outcome of the trial might have been affected.

Since the data was collected for a different research purpose, it does not provide sufficient detail about the characteristics of the participants that were supposed to be examined in this study. This has made it difficult to adequately address the objectives of this study. For example, the educational level for participants and their guardians was not captured in the original study. Therefore, educational level of household head was used instead. Lastly, verification of some data considered to have errors was a challenge because it was difficult to access the case report forms for the original trial.

5.2 Conclusion

The findings from this study show no difference in survival as well as clinical response in terms of sputum smear results at month 2 of patients with TB who received long term injectable agents at home with the help of guardians and those treated at the hospital. These findings support what was established in the original trial as no difference was observed in the successful treatment (alive and on treatment) of patients at the end of intensive phase between the two groups. Employment status was found to be significantly associated with survival of the patients. Unemployed patients were at a higher risk of dying than employed patients.

National and WHO TB recent treatment guidelines recommend the use of oral regimens in retreating patients with TB. However, total elimination of Category II regimen still relies on the availability of rapid molecular-based drug-susceptibility testing (37). Also, financial and operational issues have made oral regimens for treating patients with MDR-TB not to be into fully use at international level (37).

Taken together with previous reports, delivery of streptomycin to patients with TB by trained patient-nominated guardians in their homes is a potential workable approach for retreating patients with recurrent or drug-resistant TB in developing countries. This may provide a convenient and cost-effective approach for retreating patients with tuberculosis. The approach and may also reduce the burden that health care providers face in providing care to such patients as they are required to visit them in their homes at times.

However, use of small sample size from only two urban hospitals of Malawi, lack of blinding of the participants and medical staff, switching of critically ill patients from home-based group to the hospital arm, inadequate information on how patients selected the guardians and lack of details on how resistance to TB was assessed should be critically thought of by TB programmes when considering adoption of this option for delivery of care to patients with TB. A follow up qualitative study on assessment of the acceptability of the proposed intervention in the targeted community would help substantiate successful adoption and implementation of the discussed model of care for delivering long term TB injectable agents.

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APPENDICES

Appendix 1- Copy of ethical approval letter

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.02/13/1340 – Improving the Management of Adult Patients in Malawi on Retreatment Regime for Tuberculosis by Dr. D. Cohen

On 17 May 2013

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Approved by College of Medicine 17 MAY 2013 (COMREC) Research and Ethics Committee

Dr. G. Kalanda- Chairperson (COMREC)

17 May 2013
Date

Appendix 2- Summary of results for the data cleaning process

(serial #) ID	**Assessment**	**Diagnosis**
(10)200017	Date of death unavailable (death recorded as an outcome at month 8)	Used date treatment due to end
(20)100005	Date of death unavailable (death recorded as an outcome at month 8) Incorrect year for treatment due to end	Used date treatment due to end Changed it from 2013 to 2014
(34)200027	Defaulted at month 8	Used date treatment due to end as end of follow up period
35	Wrong date (month) for treatment to end	Changed month from November to September
(36)100181	Date of death unavailable (death recorded as an outcome at month 8)	Used discharge date as end of follow up period because date treatment due to end was also not available
(64)200059	Date for treatment due to end incorrect	Changed it from 25 July, 2014 to 25 Jan, 2015
(71)100196	Death (unsuccessful) reported as an outcome at month 2 with date of death indicated. But has fail as an outcome at month 8	Changed outcome from fail to dead at month 8
(79)100220	Defaulted as an outcome at month eight	Used date treatment due to end as end of follow up period

(82)	Wrong date (month) for treatment to end	Changed month from November to September
(88)100035	Date treatment end missing. Has cured as an outcome at month eight	Used date treatment due to end as end of follow up period
(94)100290	Date treatment end missing. Has complete as an outcome at month eight	Used date treatment due to end as end of follow up period
(114)100164	Default as outcome at month eight	Used date of end of intensive phase at end of follow up period (Date due to treatment end not available)
(117)200008	Date of death unavailable (death recorded as an outcome at month 8)	Used date treatment end as end of follow up period
(138)100004	Default as outcome at month eight	Used date due to treatment end as end of follow up period
(144)100145	Has complete as outcome at month 8 Also has date of death Date of end of intensive phase available but comes after date of death	Considered as complete with date of treatment due to end as end of follow up period
(146)100199	Year for date treatment due to end not correct	Changed year from 2014 to 2015
(159)100121	Default (unsuccessful) as an outcome at month two	Used discharge date as end of follow up period

(165)10019	Date of death unavailable (death recorded as an outcome at month 8)	Used date treatment due to end as end of follow up period
198	Wrong date (month) for treatment to end	Changed month from November to September

Appendix 3- List of Stata commands used

```
gen tbstart = date(b02dtb,"YMD")
format tbstart %td
gen tbend = date( l09dend_01,"YMD")
format tbend %td
gen lengthoffollowup = tbend- tbstart
recode n03mo8outg (1/3=2 alive) (4=1 died) (5/6=.), gen(month8)
replace month8 = 3 if month8==.
label define mo8 2 alive 1 died 3 censored
label value month8 mo8
tabulate month8
tabstat a104page , by( month8 ) stat(n mean sd p25 p50 p75)
tab a105psex month8, col row
tab b03class month8, col row
tab b04cat month8, col row
tab b18rphiv month8, col row
tab b25drink month8, col row
tab d03occ month8, col row
tab d10pmedu month8, col row
tab m03m0spr month8, col row
tab m05m2spr month8, col row
tabstat a104page, by( z07grp ) stat(n mean sd p25 p50 p75)
tab a105psex z07grp, col row
```

```
tabulate b03class z07grp, col row
tabulate b04cat z07grp, col row
tabulate b18rphiv z07grp, col row
tabulate b21smoke z07grp, col row
tabulate b25drink z07grp, col row
tabulate d03occ z07grp, col row
tabulate d10pmedu z07grp, col row
tab m03m0spr z07grp, col row
tab m05m2spr z07grp, col row
keep if z07grp ==1
tabstat a104page, by( month8 ) stat(n mean sd p25 p50 p75)
keep if z07grp ==2
tabstat a104page, by( month8 ) stat(n mean sd p25 p50 p75)
tabulate month8 a105psex if z07grp ==1, col row
tabulate month8 b03class if z07grp ==1, col row
tabulate month8 b04cat if z07grp ==1, col row
tabulate month8 b18rphiv if z07grp ==1, col row
tabulate month8 b21smoke if z07grp ==1, col row
tabulate month8 b25drink if z07grp ==1, col row
tabulate month8 d03occ if z07grp ==1, col row
tabulate month8 d10pmedu if z07grp ==1, col row
tabulate month8 a105psex if z07grp ==2, col row
tabulate month8 b03class if z07grp ==2, col row
tabulate month8 b04cat if z07grp ==2, col row
tabulate month8 b18rphiv if z07grp ==2, col row
tabulate month8 b21smoke if z07grp ==2, col row
tabulate month8 b25drink if z07grp ==2, col row
tabulate month8 d03occ if z07grp ==2, col row
tabulate month8 d10pmedu if z07grp ==2, col row
stset tbend, id(sid) origin(time tbstart ) failure( month8==1 )
stset tbend, id(sid) time0(tbstart) origin(time tbstart ) failure( month8==1 )
```

sts graph, by(z07grp)xlabel(0(50)300)ytitle(proportion alive)graphregion(fcolor(white)) risktable

sts list

stci, p(10) by(z07grp)

sts test z07grp

tabulate z07grp m05m2spr, exact

csi 0 9 1 2, exact

stcox ib2.z07grp

stcox a104page

stcox i.a105psex

stcox i.b03class

stcox i.b04cat

stcox i.b18rphiv

stcox i.b3b21smoke

stcox i.b25drink

stcox i.d03occ

stcox i.d10pmedu

stcox ib2.z07grp a104page i.a105psex i.b03class i.b04cat i.b18rphiv i.b25drink i.b21smoke i.d03occ i.d10pmedu

estat phtest, detail