BMJ Open

Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients versus risk of antimicrobial resistance (the ACT-TB Study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033999
Article Type:	Protocol
Date Submitted by the Author:	01-Sep-2019
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Keywords:	trial-of-antibiotics, Tuberculosis < INFECTIOUS DISEASES, TB, antimicrobial resistance, diagnostic performance, antibiotics

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TITLE

Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients versus risk of antimicrobial resistance (the ACT-TB Study)

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KEY WORDS

trial-of-antibiotics, tuberculosis, TB, antimicrobial resistance, AMR, antibiotics, diagnostic performance, sensitivity, specificity, randomised controlled clinical trial, randomised, RCT

Protocol version 3.0, 19 Feb 2019

ABSTRACT:

Introduction

Over 40% of global tuberculosis(TB) case notifications are diagnosed clinically without mycobacteriological confirmation. Standard diagnostic algorithms include "trial-of-antibiotics" –empirical antibiotic treatment given to mycobacteriology-negative individuals to treat infectious causes of symptoms other than tuberculosis, as a "rule-out" diagnostic test for TB. Potentially 26.5 million such antibiotic courses/year are prescribed globally for the 5.3 million/year mycobacteriology-negative patients, making trial-of-antibiotics the most common TB diagnostic, and a global-scale risk for antimicrobial resistance(AMR). Our systematic review found no randomised controlled trial(RCT) to support use of trial-of-antibiotic. The RCT aims to determine the diagnostic and clinical value and AMR consequences of trial-of-antibiotics.

Methods and analysis

A three-arm, open-label, RCT randomising(1:1:1) Malawian adults(≥18years) seeking primary care for cough into: a)azithromycin 500mg once daily for 3 days, or b)amoxicillin 1g three times/day for 5 days, or c)standard-of-care(no immediate antibiotic). We will perform Mycobacteriology tests(microscopy, Xpert/MTB/RIF and Mycobacterium-Tuberculosis culture) at baseline. We will use Audio-Computer-Assisted-Self-Interview(ACASI) to assess clinical improvement at day eight. First primary outcome will be proportion of patients reporting day-eight improvement out of those with negative mycobacteriology(specificity). Second primary outcome will be day 29 incidence of a composite endpoint of either death or; hospitalisation or; missed tuberculosis diagnosis or; HIV or tuberculosis treatment non-adherence by day 29. To determine AMR impact we compare incidence of resistant nasopharyngeal *Streptococcus pneumoniae* isolates on day 29. 400 mycobacteriology-negative participants/arm will be required to detect a ≥10% absolute difference in diagnostic

specificity with 80% power. We will estimate measures of effect by comparing outcomes in antibiotic arms(combined and individually) to standard-of-care.

Ethics and dissemination

The study has been reviewed and approved by Malawi College of Medicine Research and Ethics Committee, London School of Hygiene &Tropical Medicine Research Ethics Committee, and Regional Committee for Health and Research Ethics –Norway, and Malawi Pharmacy, Medicines, and Poisons Board.

Registration

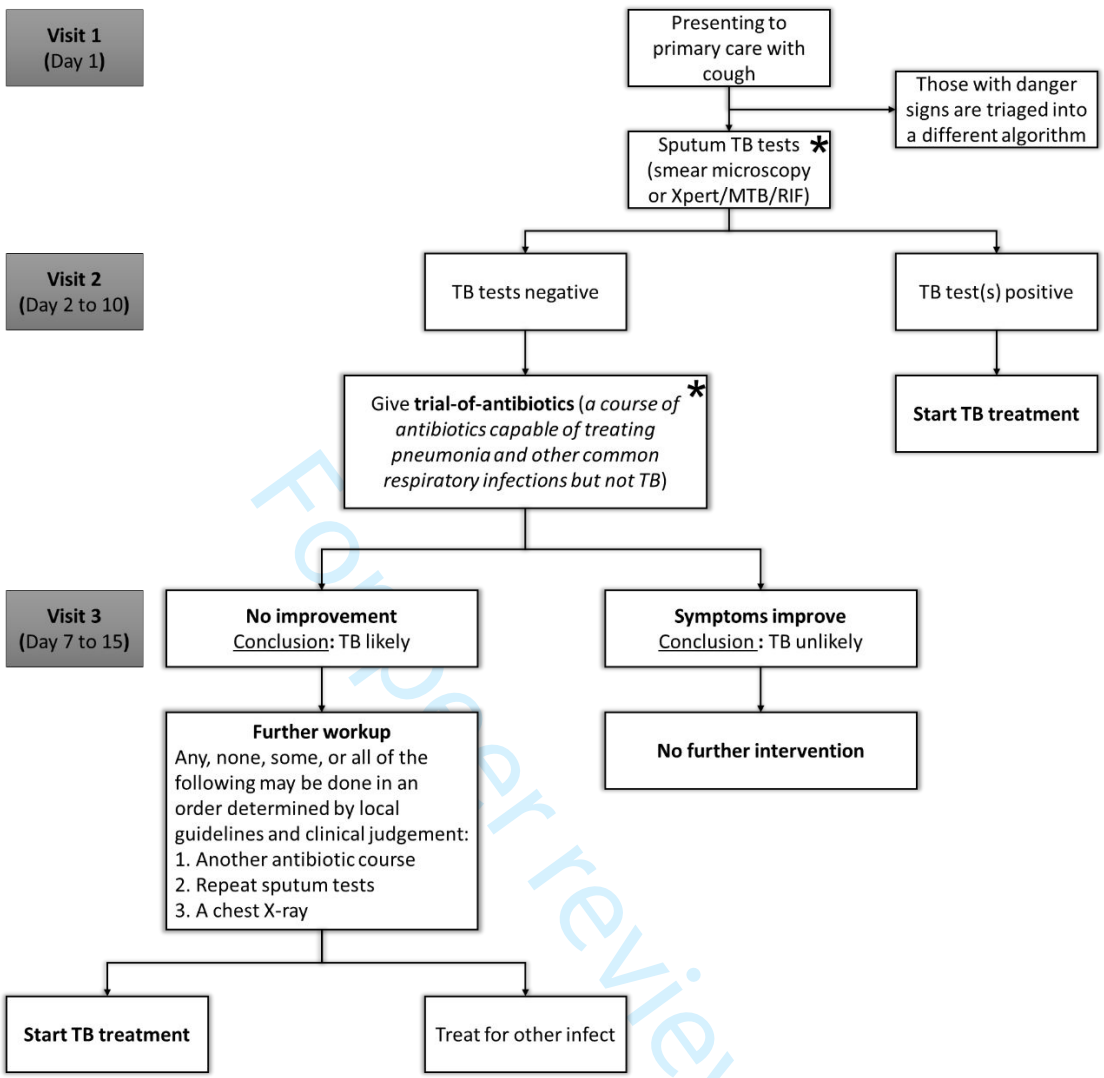
Clinicaltrials.gov, NCT03545373

Strengths and limitations

- To our knowledge this is the first randomised controlled trial to address benefits and consequences of using antibiotics as an exclusion diagnostic for tuberculosis, a widely used practice that results in millions of antibiotic prescriptions/year.
- We will also contribute evidence on AMR affecting common antimicrobials used for managing respiratory infections.
- The use of ACASI for assessing clinical response and adherence to antibiotic treatment which can be used in future studies.
- Acknowledged weakness include limited power to evaluate safety of deferred antibiotic treatment; conduct subgroup analysis by HIV status; and the possibility that participants randomised to the standard-of-care arm may find alternative access to antibiotics therefore misclassifying exposure/intervention status.

INTRODUCTION

The high case-fatality rate for tuberculosis, the leading global infectious cause of death in adults[1] with approximately 10 million cases and 1.6 million deaths in 2017,[2] in part reflects suboptimal diagnostics.[3-6] To complement diagnostic gap, standard algorithms throughout the world include a "trial-of-antibiotics" (Figure 1). This is a course of broad-spectrum antibiotics, with negligible *Mycobacterium tuberculosis* activity, given to patients with symptoms such as cough in order to "rule-out" or "rule in" tuberculosis.[7-9] In clinical practice and most national guidelines (summarised in figure 1), patients with negative sputum mycobacteriology and who have responded to antibiotic treatment are considered tuberculosis negative while those who remain symptomatic are deemed likely to have tuberculosis and undergo further evaluations leading on to receiving tuberculosis treatment.[7-9]



*The common clinical practice is that outpatients start antibiotics at the time of submitting sputum, to avoid the need for a third clinic visit to complete the algorithm.

Figure 1: The position of trial-of-antibiotics in standard algorithms for diagnosis of tuberculosis in low and middle income countries (based on the WHO GLI model guidelines and as implemented in national guidelines from Ghana, Malawi and South Africa.)

We estimate that 26.5 million courses of antibiotics are prescribed in the diagnosis of the 5.3 million smear negative tuberculosis registrations recorded annually,[10] making antibiotics the most common diagnostic for tuberculosis.[11] The 26.5 million is based on the common approach where for every one smear-negative TB case detected, five antibiotics courses are used: the first two courses of antibiotics are those given to patients who end up being registered as smear-negative tuberculosis, and the other three courses account for patients

whose symptoms resolved and tuberculosis was ruled out.[4 12] This frequency of prescription of important broad-spectrum antibiotics raises a global-scale risk for antimicrobial resistance (AMR) which like tuberculosis, is a major crisis, becoming in 2016 one of only four health topics ever to be discussed at the United Nations General Assembly.[13-16]

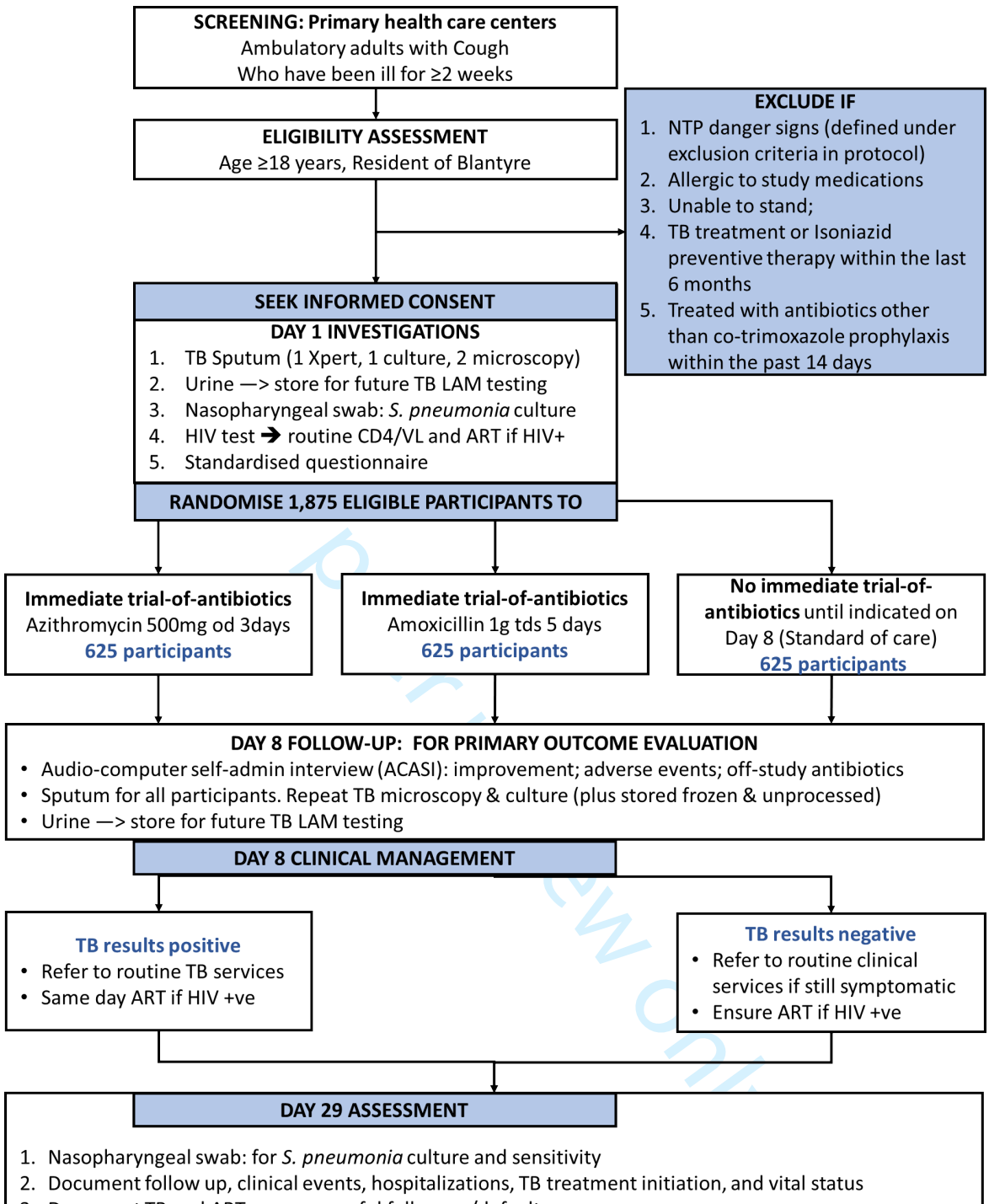
We performed a systematic literature review[17] which demonstrated that, despite being in global and national guidelines for decades, trial-of-antibiotics has limited supporting evidence base with available evidence suggesting there poor diagnostic performance.[18] None of the identified studies was an RCT and most of the observational studies were very small and not primarily designed to assess the benefits and consequences of trial-of-antibiotics. Pooled sensitivity and specificity of trial-of-antibiotics versus mycobacteriology tests were below internationally defined minimum performance profiles for TB diagnostics.

To address the evidence gaps related to a) accuracy, b) antimicrobial resistance, and c) impact on clinical outcomes of trial-of-antibiotics, we will conduct an RCT (ACT-TB Study) recruiting adult patients with cough presenting to health centres in Blantyre, Malawi. To our knowledge this is the first randomised controlled trial to rigorously address these questions.

METHODS AND ANALYSIS

Study design

This is a three-arm individually randomised (1:1:1), open-label controlled clinical trial (RCT) investigating accuracy and broader clinical, and antimicrobial resistance impact of using trial-of-antibiotics to rule-out tuberculosis among adults presenting with cough at primary care centres in Malawi (Figure 2). The trial is registered with Clinicaltrials.gov (NCT03545373).



1. ART antiretroviral treatment for HIV
2. NTP: Malawi National Tuberculosis Program
3. TB LAM: Urine Lipoarabinomannan for Tuberculosis Diagnosis
4. VL: HIV Viral load

Figure 2: Flow diagram for the clinical trial in Blantyre, Malawi

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Study setting

We will screen adults aged at least 18 years presenting to Limbe and Ndirande health centres in Blantyre, Malawi. Blantyre has an estimated tuberculosis prevalence of 1,014 per 100,000 (95% CI: 486 to 1,542), and an estimated adult HIV prevalence of 12.7% (95% CI: 11.9 to 13.6).[19]

Eligibility criteria

We will offer enrolment to patients who satisfy the following inclusion and exclusion criteria.

Inclusion Criteria

- Ambulatory clinic attendees presenting with cough
- Unwell for at least 14 days
- Aged at least 18 years
- Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period.

Exclusion Criteria

- Self-reported allergy to study medications
- WHO/Malawi National tuberculosis Program (NTP) danger signs: respiratory rate > 30/min, temperature >39^{o}C, Heart rate >120/minute, confused/agitated, respiratory distress, systolic blood pressure <90 mmHg, inability to walk unassisted
- Treated with antibiotics other than co-trimoxazole prophylaxis within the past 14 days
- Tuberculosis treatment or isoniazid preventive therapy within the last 6 months

Interventions

We will randomise participants, in a ratio of 1:1:1, to the following arms:

- **Arm 1** (Azithromycin): Azithromycin 500mg taken once daily for 3 days from enrolment day
- **Arm 2** (Amoxicillin): Amoxicillin 500 mg taken once daily for 5 days from enrolment day.
- **Arm 3** (Standard of care): No study antibiotic prescription.

Concomitant medication and interaction with other therapies

We do not have any restrictions with respect to concomitant medications apart from those listed in the exclusion criteria.

Trial restrictions

We do not require participants to have any dietary restrictions. We will also accept co-administration with contraception. Our trial interventions can safely be used in pregnancy, so we will include pregnant women should they be eligible.

Assessment of compliance

On Day-8, we will document self-reported compliance adherence of study products.

Withdraw of interventions

The investigator may also terminate a participant from study product if indicated by an adverse reaction. If a participant stops taking study product either voluntarily or by investigator decision, they will be encouraged to remain in follow up and their data will form part of intention to treat analyses.

Timing of interventions

The standard of care in national guidelines for primary care patients presenting with cough and are otherwise well (no danger signs) is to take sputum x 2 for smear microscopy or Xpert and ask them to return for results, typically 3 days - 1 week later (Figure 1). The Malawi tuberculosis diagnostic algorithm recommends use of broad-spectrum antibiotics as trial-of-antibiotics after negative sputum tests are provided to the patient, if they remain

symptomatic. Therefore, the ideal population for randomisation for this study are patients on who already have negative results for smear microscopy or Xpert. However, that may have ethical challenges considering the implications of withholding antibiotics from a symptomatic patient who may benefit from them. The first visit therefore was the most ideal time for randomisation and is in line with recommendations for test interval in investigations evaluating diagnostic tests with respect to the time interval between the index test (trial of antibiotics) and the reference test (mycobacteriology sputum sample collection). The timing also conforms to common clinical practice of prescribing trial-of-antibiotics at the same time as sputum collection to reduce diagnostic delay. The design was discussed with the District Health Office and the national TB program ahead of ethics submission.

Study outcomes

The following are descriptions of study outcomes:

Primary outcome 1: Specificity of trial-of-antibiotics versus mycobacteriology

This will be specificity of trial-of-antibiotics (the index test) in each arm against mycobacteriology tests (reference test) defined as: proportion of participants classified as tuberculosis negative (defined by self-reported day 8 improvement status of baseline symptoms) out of all who tested tuberculosis negative by mycobacteriology reference standard (smear microscopy, Xpert/MTB/RIF, or MTB culture). The mycobacteriology reference standard will be defined in participants with at least one specimen with a valid result on days 1 and 8 as tuberculosis-positive if there is at least one positive of smear microscopy, Xpert/MTB/RIF, or MTB culture; and as tuberculosis-negative if none of the tests are positive. To minimise bias, the mycobacteriology will be performed by a high-quality research laboratory in the University of Malawi College of Medicine by staff with no access to participant treatment allocation information or symptom results.

On day 8, participants will be asked the following question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?* Clinical improvement status will then be defined based on responses as tuberculosis-positive if participants report no change or worsening of illness; and as tuberculosis-negative if they report improvement. To minimise ascertainment bias in evaluation of improvement of baseline symptoms the interview will be conducted using Audio Computer Assisted Self-Interview (ACASI), a platform that allows patients to report their health state directly into a database via an audio questionnaire administered by a tablet device. We developed, piloted, and optimised the ACASI questionnaire in the study target population. Before proceeding to the self-interview, participants will be oriented using test questions until study staff are sure that they will be able to go through the interview on their own.

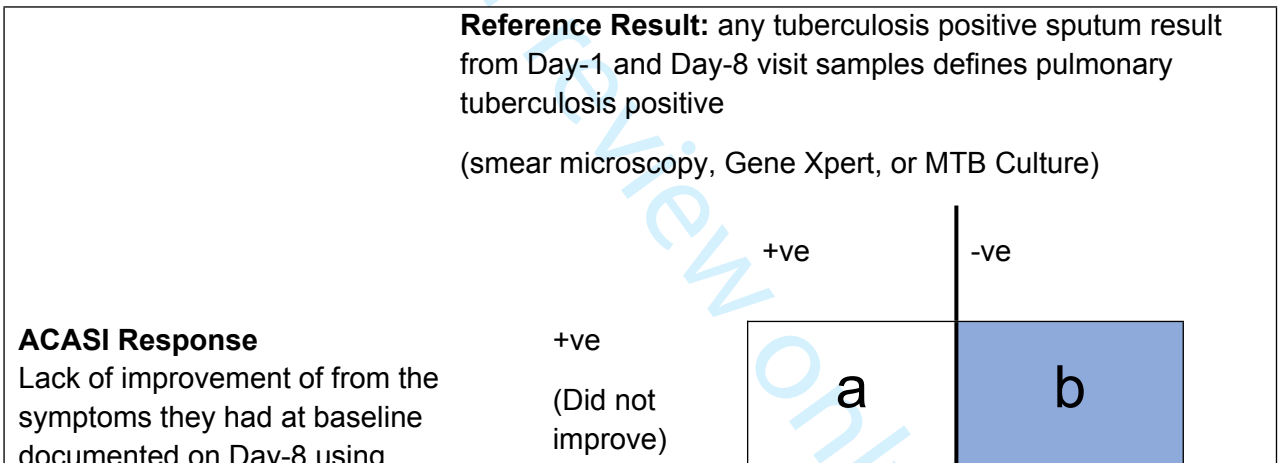

Figure 3: Ascertainment of diagnostic value of trial-of-antibiotics

Primary outcome 2: Clinical impact of trial-of-antibiotics

We will investigate the overall clinical impact of trial-of-antibiotics by comparing the day 29 risk of any of death, hospitalisation, missed tuberculosis diagnosis (untreated mycobacteriological or radiological tuberculosis identified on Day 29), and non-adherence to HIV or tuberculosis treatment (defined using responses to a questionnaire assessing adherence in the four days leading to the study visit). All these events are potential consequences of trial-of-antibiotics, grouping them as a composite endpoint appropriately represents the effect of the intervention because: 1) there are similarities in the importance patients would attach to each of the components, 2) the components occur with similar frequencies in the patient population, and 3) the direction of effect is anticipated to be the same for all.[20]

Secondary outcome 1: impact of trial-of-antibiotics on antimicrobial resistance

We will assess impact of antibiotic exposure on AMR by comparing risk of acquiring resistant isolates of *S. pneumonia* in the nasopharynx by day 29. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient window for investigating antimicrobial resistance.[21] *S. pneumonia* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract and has well documented laboratory investigation procedures in place.[22] We will exclude those with resistant isolates on both day-1 and day-29 from the numerator, as they may not truly represent incident resistance. In the denominator, we will include all randomised participants and perform analysis as intention to treat.

Secondary outcome 2: diagnostic value of trial-of-antibiotics

This will be specificity of trial-of-antibiotics (the index test assessed using ACASI) in each arm against mycobacteriology tests (reference test) defined as: proportion of participants classified as tuberculosis negative (defined by self-reported day 8 improvement status of baseline symptoms) out of all who tested tuberculosis negative by mycobacteriology reference standard (smear microscopy, Xpert/MTB/RIF, or MTB culture). Unlike in Primary

outcome 1, the mycobacteriology reference standard will extend to all study participants regardless of sputum sample availability. Participants unable to provide sputum samples, will be classified as mycobacteriologically negative. Microbiology diagnosis of tuberculosis is mainly based on sputum, therefore being unable to produce it, restricts diagnostic access, which effectively implies a negative test. We have opted to analyse this population because it is significant, can be as high as 13% of symptomatic individuals in the study setting.[23]

Secondary outcome 3: Economic evaluation

The objective of the economic evaluation is to undertake a cost-utility analysis to estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other. We will systematically compare costs and consequences associated with the interventions. We will perform a within trial comparison of the three treatment arms to estimate the incremental cost per quality-adjusted life year (QALY) gained for the azithromycin or amoxicillin arm in comparison to standard of care. Costs will be estimated from the Malawian Ministry of Health perspective. Health outcomes will be quantified in QALYs, estimated from participants' responses to the Chichewa version of the EQ-5D-3L, a Health quality of life (HRQoL) measure.[24 25] We will adopt a time horizon matching the length of participant follow-up to achieve the within trial evaluation.

Exploratory outcomes

Our exploratory analyses will be comparisons between the **azithromycin** and **amoxicillin** arms for all our primary and secondary outcomes.

Planned subgroup analyses

We will perform analysis of primary outcomes stratified by HIV status and by ART status as documented on enrolment day. This is important because the study site has high prevalence of HIV and associated bacterial infections which may be amenable to antibiotics used for trial-of-antibiotics.

Study procedures

Figure 2 and Table 1 presents the study time schedule including a summary of patient identification, baseline procedures and outcome ascertainment at day 8 and day 29 follow up visits.

Screening

Study staff will approach patients with symptoms of pulmonary tuberculosis (including cough of any duration, fever, weight loss, and night sweats) with information about the study and seek written informed consent from all patients who meet eligibility criteria. After consenting, a participant will be given a unique study identification number confirming enrolment.

Randomisation and blinding

Randomisation will be in the ratio 1:1:1 to the three arms of the trial, using block-randomisation with variable block sizes, and stratified by study site. An independent statistician will prepare the randomisation list using Ralloc command in Stata software, then print each allocation alongside a randomisation number, and seal in opaque envelopes. Upon confirming eligibility and consenting status a designated site staff will open the next available of sequentially numbered randomisation envelopes and administer the allocated study arm.

Blinding

The study will not use blinding to ensure safety of the participants and allow appropriate patient management decision-making which may be related to the trial interventions. However, all study outcome assessment will occur without reference to study treatment allocation.

Baseline procedures

At baseline, we will collect demographic data, clinical history, record vital signs, height and weight. Participants will be requested to provide two sputum samples for Xpert/MTB/RIF and two more sputum samples the following morning for smear microscopy and MTb culture. We will also collect a urine sample for lipoarabamannan antigen detection (TB LAM); and a nasopharyngeal swab for pneumococcal culture and sensitivity testing. We will offer and perform HIV testing according to the national algorithm, and link all who test positive to care. To minimise loss to follow up, we will collect contact phone numbers, a physical address and geolocation information.

Participant follow up

On day 8, the first activity (ahead of any other interaction with study staff) will be the ACASI. Other activities include providing results for day 1 tuberculosis tests and linking those who test positive to care; collection of another sputum sample for smear microscopy and *Mycobacterium tuberculosis* (MTB) culture; and management of ongoing symptoms and other illnesses. On visit day 29, the final study visit, we will document participant vital status, hospitalisations, and establish adherence to HIV and tuberculosis treatment. We will also collect nasopharyngeal swab samples from all participants, and sputum from those with tuberculosis symptoms.

Participant retention

To minimise loss to follow up, we will record geolocation information of participants' place of residence using ePAL android app, a high-resolution mapping system validated in Blantyre. We will also record up to 3 contact phone numbers of the participant and their nominated friends and relatives. We will not replace participants who discontinue study participation or study treatment regardless of reason for withdrawal or discontinuation or the time either of these occurs.

Data management

We will collect data using TeleForm (paper based system that uses optical character recognition) and Open Data Kit systems (ODK, an electronic data capture system installed on android devices). Data will be committed to a secure database located at Malawi-Liverpool Wellcome Trust (MLW) within 2 days for TeleForm, and 7 days for ODK.

319 **Table 1:** key study procedures over the study period

	STUDY PERIOD			
	Enrolment	Follow up		
TIMEPOINT	Day-1	Day-8		Day-29
ENROLMENT:				
Eligibility screen	x			
Informed consent	x			
Allocation	x			
INTERVENTIONS:				
Azithromycin	x			
Amoxicillin	x			
Standard of care	x			
ASSESSMENTS:				
Demographics	x			
History of antibiotic use	x	x		x
History & examination[1]	x	x		x
Sputum collection[2]	x	x		
Urine for TB LAM test[3]	x	x		
Nasopharyngeal swab for AMR[4]	x			x
HIV test	x			
Linking to routine care	x	x		x
ACASI[5]		x		
Clinical events[6]				x
Update contact & address		x		x

1. For symptomatic participants, Day-8 sputum mycobacteriology should be fast-tracked to inform care before they leave the clinic.
2. Give sputum bottles at end of Day-1 visit for submission on Day-8. Also collect sputum and perform mycobacteriology at any time of the study when clinically indicated
3. Urine Lipoarabinomannan for Tuberculosis Diagnosis (TB LAM)
4. Nasopharyngeal swab for S. pneumoniae culture and sensitivity as a way of determining risk of antimicrobial resistance (AMR)
5. Audio Computer Assisted Self-Interview (ACASI) for documenting change of symptoms on Day- 8 versus Day-1
6. Illnesses, clinic visits, radiological outcomes, new HIV diagnosis, new tuberculosis (TB) diagnosis, death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up

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Sample size and power

We assume that trial-of-antibiotics (in azithromycin arm or in amoxicillin arm) will correctly classify 60% of mycobacteriology negative participants (Table 2).[12] We have determined that 400 mycobacteriologically negative (true negatives) participants per arm will provide 80% power to detect a 10% absolute difference in proportion of participants without tuberculosis (mycobacteriologically negative) correctly classified as negative by trial-of-antibiotics (amoxicillin arm or by azithromycin arm) (60%) versus standard of care arm (50%) (Table 2). To determine the target enrolment that may be required to achieve 400 mycobacteriologically negative participants per arm, we first assume that 80% of participants randomised will have negative mycobacteriology,[23] requiring 500 participants to yield the 400 per arm. Assuming that 15% will not be able to produce sputum, and that 5% will not return for Day-8 visit, the sample size is increased to 625 per arm or 1,875 for the whole study.

Table 2: Power and sample size estimation for primary outcome 1

True negatives (mycobacteriology tests negative participants) b+d	[1]proportion of tuberculosis negatives correctly classified d/(b+d)	[2]effect size	power
320	0.60	0.10	69%
400	0.60	0.10	80%
480	0.60	0.10	86%

[1] specificity with either azithromycin or amoxicillin trial-of-antibiotics arms

[2]risk difference (azithromycin arm versus standard of care arm; OR amoxicillin arm versus standard of care arm; OR azithromycin arm combined with amoxicillin arm versus standard of care arm)

For the clinical impact of trial-of-antibiotics outcome, with the sample size of 625 participants/arm, and a type I alpha of 5%, we will be able to detect the difference between intervention and standard of care with 80% power, if the risk in the intervention arm is 6% or lower.

For the AMR outcome, we assume that 45% of Day-29 nasopharyngeal swabs will successfully grow *S. pneumonia,* and that 10% of the isolates will have amoxicillin or azithromycin resistance (expert evidence). Therefore, a study population of 625/arm (accounting for 10% loss to follow up to Day 29), would yield 253 isolates per arm of which 25 would exhibit amoxicillin or azithromycin resistance. For the intention to treat population (the randomised 625 participants/arm) in the standard of care arm the 25 cases of resistant isolates translate into 4% (25/625) risk. With 4% risk in the standard of care group, alpha of 0.05, and using Pearson's Chi-squared test we will be able to detect the impact of the intervention with 85% power if it leads to an increase of risk of resistant isolates from 4% to 8% (RR of 2).

Statistical approach

We will summarise the processes of recruitment including non-eligibility and reasons of exclusion in a CONSORT (Consolidated Standards of Reporting Trials) flow chart. We will describe the study participants by their baseline characteristics, by arm. We will perform analyses of all our outcomes based on an intention to treat analysis (using the arm patient was randomised to), adjusting for study site. We will report measures of effect from the following comparisons:

i) azithromycin or amoxicillin (combined) versus standard of care

ii) azithromycin versus standard of care

iii) amoxicillin versus standard of care

For primary outcome 1, and secondary outcome 2, we will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for study site. For each comparison, we will report 95% confidence intervals (CIs) and p-values from the likelihood test. If the GLM model

does not converge, we will use logistic regression to estimate the treatment effect using an odds ratio. If outcomes are rare, we will use logistic regression to model odds and report odds ratios, their associated 95% CIs, and p-values.

We will perform data cleaning and analysis using Stata release 15 (Stata Corp, College station, Texas, USA). The statistical approach will be expanded in a detailed statistical analysis plan, which will be finalised before unblinding the study data.

Monitoring and oversight

The trial will be monitored by the Research Support Centre Clinical Trials Unit of the University of Malawi College of Medicine. An independent Data and Safety Monitoring Board (DSMB), and a Trial Steering Committee (TSC) have been set up and meet bi-annually.

Trial closure

We will consider the trial closed after completing follow up of the last enrolled participant, and upon recording all mycobacteriology laboratory reports. Antimicrobial resistance lab work will continue beyond trial closure. The trial may be terminated early by the trial steering committee upon recommendation of the DSMB. The halting rule for a trial arm is an unacceptable high level of deaths assessed using an alpha determined at the first DSMB meeting.

DISCUSSION

The ACT-TB study will investigate the benefits and consequences of "trial-of-antibiotics," a widely promoted approach to many patients with suspected tuberculosis in low- and middle-income countries without solid evidence base. To our knowledge, ACT-TB Study is the first RCT of this kind. Results of our trial will improve efficiency in the approach for detecting tuberculosis (the leading infectious disease killer: ~1.6 million deaths/ year)[2] and strengthen

our fight against antimicrobial resistance (soon to be leading cause of death: ~10 million deaths/year by 2050).[26]

Choice of study interventions

We have chosen amoxicillin because it is the first line treatment for outpatient management of pneumonia in Malawi and is commonly used for trial-of-antibiotics. It also provides data of immediate programmatic relevance and a starting point to investigate exacerbation of pre-existing AMR pressure. However, amoxicillin may not demonstrate the full benefits for trial-of-antibiotics because of organisms with intrinsic ("atypicals") or acquired (common in gram-negative organisms, and *Staphylococcus aureus*) penicillin resistance.[27] Oral antibiotics that may provide the better diagnostic discrimination for bacterial vs mycobacterial causes of cough are macrolides, such as azithromycin, because of better intrinsic coverage of "bacterial causes of pneumonia including "atypical" intracellular organisms such as *mycoplasma* species,[28-30] and low levels of acquired macrolide-resistance in bacterial isolates in Malawi.[27]

ACASI for post-treatment improvement assessment

Our systematic review[18] did not identify a consistent definition of tuberculosis or no tuberculosis based on trial-of-antibiotics. A definition of clinical change following antibiotic treatment is necessary for the trial-of-antibiotics as it determines who get categorised as well or tuberculosis positive. Approaches that ranged from self-reported improvement, to a combination of clinical and radiological assessments are likely to be highly subjective and prone to bias, as well as being a potentially avoidable source of heterogeneity between studies. In this study, we hope to address these biases (particularly, inter-observer variability, and patient/interviewer reporting or ascertainment biases) by using self-rated change of illness (on day 8) recorded using a self-completed questionnaire, the ACASI (described under outcomes). The ACASI questionnaire, the delivery platform, and the

resulting data management can all be replicated in future studies, creating potential for more standardisation in assessment of clinical response to treatment.

Potential clinical impact of antibiotics

In areas with high HIV prevalence, empirical antibiotics during tuberculosis investigations could be life-saving: mortality immediately before and after tuberculosis diagnosis is high, [3 31] and is often secondary to severe bacterial infections.[31-33] The leading aetiologies of infection and death on tuberculosis treatment as well as among outpatients with tuberculosis-like symptoms are *Streptococcus pneumoniae* and non-typhoidal salmonellae: both can present with cough (primary cause) or as co-morbidities (super-infections) in patients presenting with active *Mycobacterium tuberculosis* disease.[31-33] If effective treatment of this type of life-threatening primary/super-infections reduces mortality during the diagnostic work-up of suspected tuberculosis in people living with HIV, then empirical use of broad-spectrum antibiotics would be indicated for this purpose alone, irrespective of any diagnostic contribution to tuberculosis treatment decisions. In this context, azithromycin may be the most effective arm, as salmonella infections are highly sensitive to azithromycin, but not to amoxicillin.[27]

AMR and trial-of-antibiotics

Antimicrobial resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been investigated before. Previous work has shown that empirical antibiotics can drive rapid emergence of antimicrobial resistance.[34 35] Co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010[36]. Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniae*, but with increased macrolide-resistance 6 months later.[37 38]

In this study we have the opportunity to assess the extent to which brief exposure drives antimicrobial resistance during diagnostic work-up for tuberculosis. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient window for investigating antimicrobial resistance.[21] *S. pneumonia* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract and has well documented laboratory investigation procedures in place.[22] As exploratory analyses, we will also assess nasopharygeal colonization and antimicrobial resistance in relation to tuberculosis treatment and HIV status.

Important subgroups

Response to trial-of-antibiotic- in patients with bacteriologically confirmed tuberculosis (i.e. false-negatives/low sensitivity from the perspective of tuberculosis diagnosis) may relate to multiple super-infections and so this phenomenon may vary by HIV status, since multiple concurrent infections are a hallmark of advanced HIV immunosuppression, and commonly identified in patients with suspected tuberculosis in the pre-ART era.[4 32] More recently, in Malawi, 45% of adults who presented to primary care with prolonged cough (≥2 weeks) were HIV-positive, of whom only ~20% started tuberculosis treatment on the basis of positive mycobacteriology.[23] As such, the benefits and consequences of trial-of-antibiotics may vary by HIV status and by subsequent tuberculosis treatment decisions. We will, therefore, include a pre-specified sub-analysis of trial outcomes stratified by HIV and ART status.

ETHICS AND DISSEMINATION

The study has been reviewed and approved by the University of Malawi College of Medicine Research and Ethics Committee (COMREC), the London School of Hygiene & Tropical Medicine Research Ethics Committee, and Regional Committee for Health and Research Ethics, NTNU-Midt, Norway. Regulatory approval has been granted by the Malawi Pharmacy, Medicines, and Poisons Board (PMPB). We will present any future protocol

modifications to these bodies before implementing. We will submit results for publication in a peer-reviewed journal. We will submit abstracts to relevant national and international conferences. This study will follow the standards set by CONSORT guidelines.

AUTHORS' CONTRIBUTIONS

THD, KF and ELC are the main contributors to the study design and conception. All authors carefully reviewed and substantially contributed to the development of the protocol. THD developed the first draft of the manuscript. All authors reviewed and contributed to the manuscript. All authors read and approved the final manuscript. THD is the guarantor for this work.

FUNDING AND SPONSORSHIP STATEMENT

The clinical trial is funded by the Commonwealth Scholarship Commission and the Helse Nord RHF grant awarded to THD. This work is part of THD's PhD work at London School of Hygiene & Tropical Medicine (LSHTM). LSHTM is the sponsor of this clinical trial (sponsor address: Keppel Street, Bloomsbury, London WC1E 7HT). ELC is funded by a Wellcome Trust Senior Research Fellowship in Clinical Science: WT200901. The funding agencies and the sponsor had no role in the preparation of the protocol or the intention to submit this manuscript for publication.

COMPETING INTERESTS STATEMENT

We have no conflicts of interest to declare.

PATIENT AND PUBLIC INVOLVEMENT

Patients were involved in the design of the study especially the audio-computer-assisted interview (ACASI) used for collecting primary outcome data. Health workers were involved in the design of study visits and patient flow.

BODY WORD COUNT: 4,034

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Susceptibilidad a macrólidos de aislados bacterianos provenientes de infecciones adquiridas en la comunidad. *Tropical Medicine & International Health* 2011;16(10):1192-205. doi: 10.1111/j.1365-3156.2011.02837.x

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APPENDIX 1: TRIAL REGISTRATION—DATA SET

NCT Number	NCT03545373
Title	Accuracy and Consequences of Using Trial-of-antibiotics for TB Diagnosis (ACT-TB Study)
Acronym	ACT-TB
Status	Recruiting
Study Results	No Results Available
Conditions	Tuberculosis|Respiratory Tract Infections|Pneumonia
Interventions	Drug: Azithromycin|Drug: Amoxicillin
Outcome Measures	Diagnostic accuracy of trial-of-antibiotics: Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 against a mycobacteriology reference standard.|Overall clinical benefit of empirical antibiotic treatment in primary care participants with chronic cough: proportion of participants experiencing adverse clinical outcomes|Impact of trial-of-antibiotics on antimicrobial resistance|Diagnostic accuracy of trial-of-antibiotics including participants who did not produce sputum|Economic analysis of use of trial-of-antibiotics
Sponsor/Collaborators	London School of Hygiene and Tropical Medicine|University of Malawi College of Medicine
Gender	All
Age	18 Years and older Â (Adult, Older Adult)
Phases	Phase 3
Enrollment	1875
Funded Bys	Other
Study Type	Interventional
Study Designs	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Diagnostic
Other IDs	15232
Start Date	February 25, 2019
Primary Completion Date	Jun-20
Completion Date	Jun-20
First Posted	June 4, 2018
Results First Posted	
Last Update Posted	August 15, 2019
Locations	University of Malawi College of Medicine, Blantyre, Southern, Malawi
Study Documents	
URL	https://ClinicalTrials.gov/show/NCT03545373

APPENDIX 2: FULL TRIAL PROTOCOL

(attached separately)

APPENDIX 3:PATIENT INFORMATION SHEET AND INFORMED CONSENT

(attached separately)

APPENDIX 4: ETHICS AND REGULATORY APPROVALS

(attached separately)

01 September 2019

The Editor in Chief
BMJ Open
BMJ Open Editorial Office
BMA House, Tavistock Square
London, WC1H 9JR, UK

Dear Editor,

RE: Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients versus risk of antimicrobial resistance (the ACT-TB Study)

We are pleased to submit a clinical trial protocol bearing the above title for consideration for publication in *BMJ Open*. This clinical trial aims to address a critical, yet ignored, intersection between two major global challenges: 1) the suboptimal nature of Tuberculosis diagnostics, perhaps the key underlying driver for the high mortality in this top killer of all infectious disease; and 2) antimicrobial resistance, which currently kills 700,000 people per year and if left unchecked, it will surpass all killers with deaths from untreatable infections catapulting to 10,000,000 per year by 2050. It is therefore not surprising that Tuberculosis and antimicrobial resistance are two of only five health issues to have ever secured a United Nations High Level Meeting.

Inspired by our recently-submitted, and under-publication-consideration systematic review (*Divala TH, Fielding KL, Nliwasa M, Sloan DJ, Gupta-Wright A, Corbett EL. Sensitivity and specificity of using trial-of-antibiotics versus sputum mycobacteriology for diagnosis of tuberculosis: protocol for a systematic literature review. Systematic reviews. 2018 Dec;7(1):141.*), we describe how we will investigate benefits and consequences of the current practice using broad-spectrum antibiotics (such as amoxicillin, macrolides, and others used for treating bacterial pneumonia) as Tuberculosis diagnostics. The use of antibiotics in TB diagnostic algorithms is a practice that is grounded on limited evidence, yet results in prescriptions of approximately 26.5 million antibiotic courses.

Administration of a course of broad spectrum antibiotics as a means of ruling out tuberculosis in coughing patients with negative sputum TB tests, has been part of the TB diagnostic algorithm for over 20 years. In this practice, known as trial-of-antibiotics, response to the antibiotics is interpreted as a negative test for Tuberculosis while failure to respond increases the probability of Tuberculosis, warranting further Tuberculosis diagnostics. Getahun and colleagues (Lancet. 2007;369(9578)]

provide what is perhaps the best description of this approach and extent of use in sub Saharan Africa, **but to our knowledge, no comprehensive assessment of diagnostic accuracy of trial-of-antibiotics exists. Despite the wide application and potential consequences, no clinical trial or systematic review has been done on the subject.**

Our review and meta-analysis has established that the current policy and practice regarding trial-of-antibiotics has weak evidence base, poor diagnostic performance, and worryingly inconsistent choice of antibiotics, number of antibiotic courses, and interpretation of test outcomes. **We believe that this manuscript is appropriate for publication in this special issue because it has potential to 1) drive research forward, 2) help optimize TB diagnostic algorithms with current and new diagnostics, and 3) to improve clinical care and treatment outcomes in the entire TB high burden world.** This work essentially cross-cuts the ideals of the *BMJ Open*.

Ethics and regulatory approvals

The protocol has been reviewed and approved by the following bodies:

1. University of Malawi College of Medicine Research and Ethics Committee (COMREC),
2. London School of Hygiene & Tropical Medicine Research Ethics Committee
3. Regional Committee for Health and Research Ethics, NTNU-Midt, Norway
4. The Malawi Pharmacy, Medicines, and Poisons Board (PMPB)
5. Annual approvals are granted by 1 and 2

No part of this manuscript has been published or is under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you for considering our manuscript.

Sincerely,

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PARTICIPANT INFORMATION SHEET

Participant information sheet

What is the benefit and unintended consequences of using antibiotic treatment as a way of excluding tuberculosis disease in patients with cough?

Introduction

We would like to invite you to take part in a research study. Joining the study is entirely up to you. Before you decide, you need to understand why the research is being done and what it would involve. One of our team will go through this information sheet with you, and answer any questions you may have. Ask questions if anything you read is not clear or you would like more information. Please feel free to talk to others about the study if you wish. Take time to decide whether or not to take part.

What is the purpose of the study?

Tuberculosis (TB) is a disease that causes a long illness and cough with sputum. Although curable TB is difficult to detect. When they fail to detect TB after testing sputum, clinicians give antibiotic treatment that can cure all other causes of TB symptoms but not TB. In this approach, TB is considered ruled out if patient gets better and it is considered likely if they do not get better. The goal of this research study is to develop understanding of how well the antibiotics help distinguish TB patients from those who do not have it, whether giving antibiotics carries other health benefits, and whether it leads to development of disease causing organisms which are resistant to drugs.

We will learn about this by comparing a group of patients given antibiotics on the first day of the study to another group not given antibiotics. There will be two groups receiving antibiotics as follows: 1) Azithromycin taken as one tablet once a day for 3 days, and 2) Amoxicillin 4 capsules taken three times a day for 5 days. The group you will go into, out of the three, will be decided by chance so you can fall into any group.

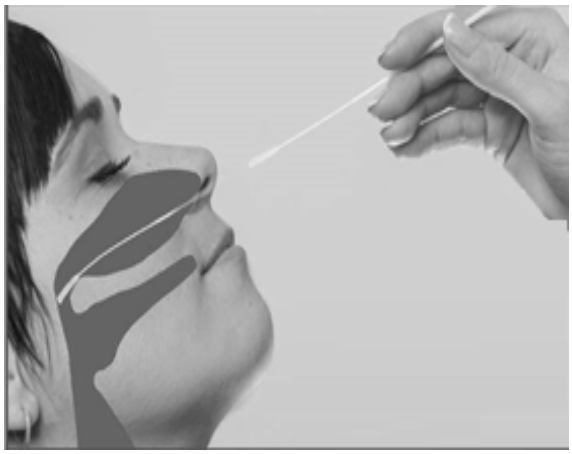
What will be involved if I accept to participate in the study?

We are considering you for participation in this study because you told us that you have a cough. Any patient who has been coughing for at least 2 weeks, is at least 18 years, and lives within Blantyre, is eligible to participate in this study if they do not have signs consistent with serious illness. Apart from you, we will recruit 1,874 other individuals.

Study activities will be performed the first day, at 1 week (Day 8), and at one month (Day 29). At each of these study visits, we will ask you questions about your contact details, your health, use of medications, and any illnesses or hospitalisations you may have had in between study visits. We will also document relevant details from your health passport and other clinical documentation you may have.

On Day 1 and at 1 week, we will ask you to submit sputum and urine samples for TB tests. If you are not able to give sputum on Day 1, we will give you containers so that you can bring them the following morning. Some of the sputum TB tests results will become available after 7 days and we will pass them to health center clinicians who will make a plan for your care, the other results may take up to 4 weeks so you will get them at the 1 month visit. Urine TB test results will not be available for your clinical care.

We will also do an HIV test. If the results are confirmed to be HIV positive we will do a viral load test, and at the end of the study activities on Day 1, we will link you to HIV management team here at the health center who will start you on treatment. Should we make a diagnosis of TB or HIV at any other point during the study, we will link you with the responsible health center team for treatment services.



On day 1 and at 1-month visit, we will swab the back of the inside of your nose as shown in this picture to collect germs that live there. We will test the germs for drug resistance. Results of this test are not relevant to your care.

On 1-week visit, we will ask you to report how your health has changed in comparison to how you were on day 1. These questions will be read to you by a computer and you will answer them by choosing various options which it will display during the interview.

The 1 month visit will be the final study visit where we will also provide you with results for TB culture and ask if you have TB symptoms. If you are in HIV or TB care, we will ask how your follow up is going. The appointment with you at 1 months is very important because it will help you to know the results of the TB tests and it will also help us know the status of your health.

The number of clinic visits you will make for this study is at least three. Here we count Day 1, one visit after one week, and another visit at one month. If you have not been able to come here for any of the visits, we will remind you by phone call or we will use the permission and information you will give us to visit you at your home. The first visit will take about 60 minutes and the later visits will take about 30 minutes each.

Will there be any risks involved in this study?

This study is a low risk study. There are no risks involved in submitting sputum or urine for the study. You may feel some discomfort during swabbing of the back of the nose and during blood collection for HIV and viral load tests. Azithromycin and amoxicillin are already widely used in Malawi and rarely cause problems. Rare side effects for azithromycin include feeling nervousness, skin reactions and disturbance of heart function. Rare side-effects for amoxicillin are mental state changes, feeling light-headed, and reactions to sunlight.

The London School of Hygiene and Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation.

Will there be any benefits in this study?

The key benefit of this study is that you will have access to a more detailed TB evaluation process than usual. This will help you know if you have TB and to have the opportunity to start TB treatment. The study is also beneficial to health care providers because it will address important questions about use of antibiotics during the TB diagnostic process.

Will the findings in the study be confidential?

Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you. Information about TB test result and HIV test results will be recorded using an identification number. However, any records or data obtained as a result of your participation in this study may be used by LSHTM who are sponsoring this study, regulators of health research (COMREC), or by members of the research team. These records will be kept in a locked space in the University of Malawi College of Medicine. Information and samples collected in this study will be retained for up to 10 years after the end of the trial, according to our institution recommendations. These collected samples and other information may also be used for future studies if you give us that consent.

Can I withdraw from the study anytime and will this affect my treatment?

You are free to choose whether or not to participate in this study. While we would like you to participate in the study to the very end, withdrawing at any point is an option that is freely available to you without any penalty or loss of any entitled benefits. You will be provided with any significant new findings developed during the course of this study that may relate to or influence your willingness to continue participation.

What are the financial benefits of participating in this study?

There will be no payment given to you for participating in the study. The study will provide at least MK8,000 as compensation for your costs of attending the study visits. We will give this money in instalments on scheduled study visits.

Is this study approved by an ethics committee?

The study has been approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, and the College of Medicine Research Ethics Committee (COMREC).

Who do you ask if you have questions regarding the study?

If you have any questions concerning participation in this study, please feel free to ask me. Alternatively, you can contact the following people by phone or post:

	Name	Telephone	Postal address
Study investigators	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi
	Dr Marriott Nliwasa	0888681948	
COMREC			
	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

What is the benefit and unintended consequences of using antibiotics treatments as a way of excluding tuberculosis disease in patients with cough?

Patient declaration

Statement	Initial or thumbprint each box
I confirm that I have read the above information sheet for the above named study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. OR I have had the information explained to by study personnel in a language that I understand. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from LSHTM, University of Malawi College of Medicine, and COMREC, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that data about me may be shared via a public data repository or by sharing directly with other researchers, and that I will not be identifiable from this information	
I understand that the tissue sample collected from me will be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects	
I agree to take part in the above named study	

Printed name of participant	**Signature/thumb print of participant**	**Date**
Printed name of impartial witness*	**Signature of impartial witness***	**Date**

I attest that I have explained the study information accurately to _____, and was understood to the best of my knowledge by, the participant and that he/she has freely given their consent to participate* in the presence of the above named impartial witness (where applicable).

Printed name of staff obtaining consent	**Signature of staff obtaining consent**	**Date**

*Impartial witness should be someone the participant trusts. The impartial witness can write the participant name but cannot sign for them. Instead, illiterate participants should use thumbprint in place of signature and the impartial witness should go ahead and sign in designated space.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PARTICIPANT INFORMATION SHEET

Chikalata chofotokozera ofuna kutenga nawo mbali

Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufifuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

Chiyambi

Tikukukupemphani kuti mutenge nawo mbali mu kafukufuku. Ndi chifuniro chanu kulowa mu kafukufukuyu. Musanapange chiganizo, mukuyenera kumvetsa chifukwa chimene kafukufukuyu akuchitikira komanso zimene zitadzachitike. M'modzi mwa anthu a gulu logwira ntchito mu kafukufuku awerenga chikalatachi pamodzi ndi inu, ndipo ayankha mafunso ena aliwonse amene mungakhale nawo. Funsani mafunso ngati simukumvetsa zomwe mwawerenga kapena ngati mukufuna uthenga owonjezera. Muli omasuka kulankhula ndi ena zokhudza kafukufukuyu ngati mukufuna. Ganizani mofatsa musanavomereze kutenga nawo mbali kapena ayi.

Kodi cholinga cha kafukufukuyu ndi chiyani?

Chifuwa chachikulu (TB) ndi matenda amene munthu amkhala chidwalire kwa nthawi yaitali. Odwalayo, amapanga makhololo. Ngakhale chili chochizika, chifuwa chachikulu ndi chovuta kuchipeza. Pamene njira zoyeza makholoro zalephera kupeza chifuwa chachikulu, achipatala amapereka mankhwala opha tizirombo toyambitsa matenda amene angathane ndi zonse zimene zimayambitsa zizindikiro za matenda ofanana ndi chifuwa chachikulu. Ngati odwala apeza bwino ndi njira imeneyi amaganiziridwa kuti alibe matenda a chifuwa chachikulu koma ngati sanapeze bwino amaganiziridwa kuti ali ndi chifuwa chachikulu. Cholinga cha kafukufuku ameneyu ndi kufuna kumvetsa za m'mene mankhwala amenewa amathandizira kusiyanitsa odwala matenda a chifuwa chachikulu ndi amene alibe matendawa, ngati mankhwalawa ali ndi phindu lina kwa odwala, komanso ngati kupereka mankhwalawa kukubweretsa tizirombo tosamva makhwala.

Tiphunzira zimenezi pakusiyanitsa gulu la anthu odwala amene apatsidwa mankhwala opha tizirombo toyambitsa matenda patsiku loyamba la kafukufukuyu ndi gulu lina limene silinapatsidwe mankhwalawa. Pakhala magulu awiri olandira mankhwala opha tizirombo motere: 1) Azitrhomycin omwedwa pilisi imodzi kamodzi patsiku kwa masiku atatu, komanso 2) Amoxicillin makapusolo anayi omwedwa katatu patsiku kwa masiku asanu. Gulu limene mulowe, mwa magulu atatuwa, lisankhidwa mwa mayere choncho mukhoza kupezeka mu gulu lina lirilonse.

Kodi chidzachitike ndi chiyani ngati ndingavomereze kutenga nawo mbali mu kafukufukuyu?

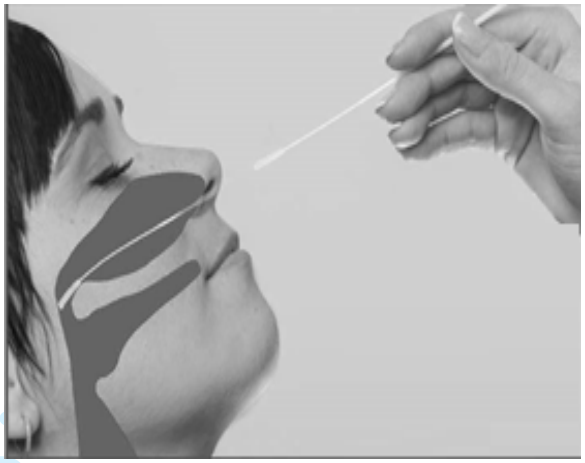
Tikukupemphani kuti mutenge nawo mbali mu kafukufukuyu chifukwa mwatiuza kuti muli ndi chifuwa. Odwala wina aliyense amene wakhala akukhosomola kwa masabata osachepera awiri, ali ndi zaka zosachepera 18, ndipo amakhala mu Blantyre muno, atha kutenga nawo mbali mu kafukufukuyu ngati alibe zizindikiro zosonyeza kudwalika kwambiri. Kupatula inu, tilemba anthu ena okwanira 1,874.

Zochitika za kafukufukuyu zidzapangidwa patsiku loyamba, pa sabata imodzi (Tsiku 8), ndi pamwezi umodzi (Tsiku 29). Pa masiku a kafukufuku onsewa, tidzakufunsani mafunso okhudzana ndi m'mene tingalumikizirane nanu, thanzi lanu, kagwiritsidwe ntchito ka mankhwala, ndi matenda ena aliwonse kapena kugonekedwa mu chipatala komwe kungakuchitikireni. Tidzalembansoo zinthu zofunikira

kuchokera mu bukhu lanu la kuchipatala komanso zolembedwa zina za chipatala zimene mungakhale nazo.

Patsiku loyamba ndi pakutha pasabata yoyamba, tidzakufunsani kuti mupereke makhololo komanso mkodzo pofuna kuyeza matenda a chifuwa chachikulu. Ngati simungakwanitse kupereka makhololo patsiku loyamba, tidzakupatsani mabotolo kuti mudzawabweretse m'mawa wa tsiku lotsatira. Zotsatira zina za makhololo zidzatuluka pakutha pa masiku asanu ndi awiri ndipo tidzazipereka kwa matodolo a chipatala chino kuti akuthandizeni, zotsatira zina zidzatenga pafupi-fupi masabata anayi choncho mudzazilandira pa ulendo wa pamwezi umodzi. Zotsatira zanu zoyesa mikodzo ku matenda a chifuwa chachikulu sizidzakhalapo ku nkhani ya chisamaliro chanu cha kuchipatala.

Tidzayezanso kachirombo ka HIV. Ngati zotsatirazi zasonyeza kuti muli ndi kachirombo ka HIV tidzayeza kuchuluka kwa tizirombo ta HIV, komanso kukutumizani kolandilira chithandizo chamatendawa. Ngati tingakupezeni kuti muli ndi matenda a chifuwa chachikulu kapena kachirombo ka HIV panthawi ina iliyonse mkati mwa kafukufukuyu, tidzakutumizani kolandilira zithandizo zamatendawa pompano pachipatala.



Patsiku loyamba komanso pa ulendo wa mwezi woyamba, tidzapukuta kumbuyo kwa mkati mwa mphuno mwanu ngati m'mene zikuonekera pachithunzichi kuti titenge tizirombo timene timakhala m'menemo. Tidzayeza tizirombo timeneti kuti tione ngati tikumva mankhwala. Zotsatira zimenezi sizidzagwiritsidwa ntchito kuchisamaliro chanu chaku chipatala.

Pa ulendo wa sabata yoyamba, tidzakupemphani kuti mutiuze m'mene thanzi lanu lasinthira kuyerekeza ndi m'mene munaliri patsiku loyamba. Mafunso amenewa adzawerengedwa kwa inu kudzera pa makina a kompyuta ndipo mudzawayankha pakusankha mayankho angapo amene makinawa adzawonetse panthawi yomwe azidzafunsa.

Ulendo wa pa mwezi umodzi udzakhala wotsiriza umene tidzakupatseninso zotsatira za zoyesa za matenda a chifuwa chachikulu komanso tidzakufunsani ngati muli ndi zizindikiro za matenda a chifuwa chachikulu. Ngati panthawiyi mudzakhale kuti mukulandira Thandizo la HIV kapena TB, tidzakufuna kudziwa kuti zikuyenda bwanji. Kukumana ndi inu patatha mwezi umodzi ndikofunikira kwambiri chifukwa zidzakuthandizirani kuti mudziwe zotsatira za zoyeza za matenda a chifuwa chachikulu ndipo zidzatithandiziranso kudziwa zam'mene thanzi lanu liliri.

Maulendo a kuchipatala amene mudzayende a kafukufukuyu ndiwosachepera atatu. Pamenepa tikuwerenga tsiku loyamba, ulendo umodzi pakutha pa sabata imodzi, ndi ulendo umodzi pa mwezi umodzi. Ngati simunakwanitse kubwera kuno pa ulendo wina uliwonse tidzakukumbutsani pokuyimbirani lamya kapena tidzagwiritsa ntchito chilorezo ndi uthenga umene mudzatipatse kuti tikuyendereni kunyumba kwanu. Patsiku loyamba tidzakhala nanu kwa mphindi makumi asanu ndi imodzi, pamene paasiku ena onse, tidzakhala nanu kwa mphindi makumi atatu.

Kodi padzakhala ziopsezo zina zilizonse zochitika mu kafukufukuyu?

Kupanga nawo kafukufukuyu sikuika moyo wanu pa chiopsyezo chochuluka. Palibe chiopsezo pa kupereka makhololo kapena mikozo mu kafukufukuyu. Mukhoza kusamva bwino panthawi yopukuta kumbuyo kwa mphuno komanso panthawi yotenga magazi oyeza za kachirombo ka HIV ndi kuchuluka kwa tizirombo toyambitsa matendawa. Azithromycin ndi amoxicillin ndi mankhwala oti akhala akugwiritsidwa ntchito kwa nthawi yayitali m'Malawi ndipo sikweni-kweni kuyambitsa mavuto. Patali-patali azithromycin amapangitsa kumva nthumazi, ziwengo, komanso kusokonekera kwa kagwiridwe ntchito ka mtima. Patali-patali amoxicillin amapangitsa kusakhazikika mmanganizo, kumva chizungulire, komanso kutuluka ziwengo munthu akakhala padzuwa.

A London School of Hygiene ndi Tropical Medicine ali ndi thumba landalama zachipukuta misozi lokhudzana ndi kafukufukuyu. Ngati mwapweteka kapena kuvulala chifukwa chotenga nawo mbali mu kafukufukuyu, mudzakhale omasuka kupempha chipukuta misonzi.

Kodi padzakhala zopindula zina zilizonse mu kafukufukuyu?

Chopindulitsa chodziwika cha kafukufukuyu ndi chakuti mudzakhala ndi mwayi oyezedwa matenda a chifuwa chachikulu mozama kuposa m'mene zimakhalira nthawi zonse. Zimenezi zidzakuthandizirani kudziwa ngati muli ndi matenda a chifuwa chachikulu komanso kukhala ndi mwayi oyamba kulandira thandizo la mankhwala a chifuwa chachikulu. Kafukufukuyu ndi opindindulitsanso kwa opereka chisamaliro cha kuchipatala chifukwa adzayankha mafunso ofunikira okhudzana ndi kagwiritsidwe ntchito ka mankhwala opha tizirombo toyambitsa matenda panthawi ya ndondomeko yoyeza matenda a chifuwa chachikulu.

Kodi zotsatira za mukafukufukuyu zidzakhala za chinsinsi?

Chizindikiritso chanu mu kafukufukuyu chidzatengedwa kukhala cha chinsinsi. Zotsatira za kafukufukuyu, zikhoza kudzasindikizidwa ndi cholinga cha sayansi koma dzina lanu kapena chizindikiritso chilichonse chokhudzana ndi inu chidzabisidwa. Uthenga okhudza zotsatira zoyesa matenda achifuwa chachikulu kapena HIV zidzalembedwa pogwiritsa ntchito nambala yanu yakafukufuku. Komabe, zina zomwe mungatifotokozere zitha kudzagwiritsidwa ntchito ndi amene ali oyang'anira za kafukufuku wa zaumoyo (COMREC) komanso LSHTM. kapena ndi mamembala a gulu la kafukufukuyu. Zolembedwazi zidzasungidwa mumalo otsekedwa bwino ku sukulu ya ukachenjede ya Malawi College of Medicine. Uthenga ndi zoyesa zotengedwa mu kafukufukuyu zidzassungidwa kwa zaka pafupi-fupi khumi (10) pakutha pakuyesaku, malingana ndi ndondomeko ya bungwe lathu. Zoyesa zotengedwazi ndi mauthenga ena zikhoza kugwiritsidwanso ntchito pa kafukufuku wamtsogolo ngati mutatipatsa chilolezo chimenecho.

Kodi ndikhoza kusiya kafukufukuyu nthawi ina iliyonse ndipo zimenezi zingadzakhudze thandizo langa la mankhwala?

Muli ndi ufulu kusankha kutenga nawo mbali kapena kusatenga nawo mbali mu kafukufukuyu. Ngakhale tingakonde kuti mutenge nawo mbali mu kafukufukuyu mpaka ku mapeto, kutuluka nthawi iliyonse mukafukufuku ndi chisankho chanu popanda chilango chilli chonse kapena kuluza kulandira thandizo lililonse lomwe mukuyenera kulandira. Munthawi yakafukufukuyu, tidzakudziwitsani patati

patuluka mauthenga ena a sayansi ofotokoza zinthu zimene zingakupangitseni kuti mulingalirenso zachisamkho chanu chotenga nawo mbali.

Kodi pali phindu la ndalama lotani pakutenga nawo mbali mu kafukufukuyu?

Sipadzakhala kupatsidwa malipiro chifukwa chotenga nawo mbali mukafukufukuyu. Ndalama yomwe tidzakupatseni ndi yokwana MK8,000. Ndalamayi tizikupatsani pangonopango pamasiku anu akafukufuku..

Kodi kafukufukuyu ndiwovomerezeka ndi komiti yowona za ufulu wa anthu mukafukufuku?

Kafukufukuyu wavomerezedwa ndi London School of Hygiene & Tropical Medicine Research Ethics Committee, ndi College of Medicine Research Ethics Committee (COMREC).

Kodi mungafunse ndani ngati muli ndi mafunso okhudzana ndi kafukufukuyu?

Ngati muli ndi mafunso ena aliwonse okhudza kutenga nawo mbali mukafukufukuyu, chonde khalani omasuka kundifunsa. Munjira ina, mukhoza kulumikizana ndi anthu otsatirawa pa lamya kapena polemba kalata kumakeyala awa:

	Name **Dzina**	**Telephone** **Lamya**	**Postal address** **Adilesi**
Study investigators Akulu-akulu akafukufuku	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine
	Dr Marriott Nliwasa	0888681948	Private Bag 360, Chichiri, Blantyre 3, Malawi
COMREC	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

Kodi pali phindu lotani komanso zotsatira zosayembekezereka zotani pogwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ngati njira yothana ndi matenda a chifuwa chachikulu mu anthu amene ali ndi chifuwa?

Chitsimikizo cha odwala

Lembani mubokosi liri kumanjali mawu oyamba adzina lanu kapena dindani ndi chala ngati mukuvomereza

Mfundo yachitsimikizo	
Ndikutsimikiza kuti ndawerenga chikalata cha uthenga wa kafukufuku amene watchulidwa m'mwambamu. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira. KAPENA Ndafotokozeredwa uthengawu ndi akafukufuku mu chilankhulo chimene ndikuchimvetsa. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira.	
Ndikumvetsa kuti kutenga nawo mbali kwanga ndikosakakamizidwa ndipo ndili ndi ufulu kusiya panthawi ina iliyonse popanda kupereka chifukwa china chilichonse, popanda kukhudza chisamaliro cha kuchipatala kapena ufulu wanga.	
Ndikumvetsa kuti magawo ofunikira a zolembedwa zanga za ku chipatala komanso mu kafukufukuyu kuwonedwa ndi anthu ovomerezeka aku LSHTM, University of Malawi College of Medicine komanso COMREC, pamene kuli kofunika kutenga nawo mbali mukafukufukuyu. Ndikupereka chilolezo kwa anthu amenewa kuti athe kuwona za zolembedwa zanga.	
Ndikumvetsa kuti zomwe atolere akafukufuku zokhudza ine zikhoza kugawilidwa kwa anthu ena opanga kakafukufuku, ndipo kuti sipadzakhala chizindikiro chilichonse chosonyeza kuti zinachokera kwa ine.	
Ndikumvetsa kuti zoyeza za mthupi mwanga zimene zidzatengedwe kwa ine zidzagwiritsidwa ntchito kuthandizira kafukufuku wina mtsogolo, ndipo zikhoza kudzagawidwa mwachinsinsi ndi akafukufuku ena, pa ntchito yawo yovomerezeka ndi malamulo aowona zakafukufuku.	
Ndikuvomereza kutenga nawo mbali mu kafukufuku amene watchulidwa pamwambayu.	

Dzina la wotenga nawo mbali **Sayini/chidindo cha chala cha wotenga mbali** **Tsiku**

Dzina la mboni yopanda mbali* **Sayini ya mboni yopanda mbali** **Tsiku**

Ndikutsimikiza kuti ndafotokoza za uthenga wa kafukufukuyu molondola kwa _____, ndipo ine zinamveka monga mwakudziwa kwanga ndi, wotenga nawo mbali komanso kuti apereka chilolezo chawo kuti atenge nawo mbali* pamaso pa mboni yopanda mbali imene yatchulidwa pamwambapa (ngati kuli koyenera).

Dzina la wotenga chilolezo **Sayini ya wotenga chilolezo** **Tsiku**

*Mboni yopanda mbali ikuyenekera kukhala yokhulupiridwa ndi munthu ofuna kutenga nawo mukafukufukuyo. Mboni ikhoza kulemba dzina la munthu ofuna kutenga nawo mukafukufukuyo koma siingasayine mmalo mwake. Munthu ofuna kutenga nawo mukafukufuku, ngati samatha kuwerenga ndi kulemba, asayine ndi chidindo cha chala chake ndipo mboni isayine dzina ndi sayini. pamalo ambone.

Mpatseni otenga nawo mbali chikalata chimodzi kuti chikhale chake

Dzina la kafukufuku: Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufufuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

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.04/18/2381 - Accurancy and Consequences of using Trial-of-antibiotics for TB diagnosis (ACT-TB Study) by Titus H Divala

On 03-Jul-18

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

03-Jul-18

Dr. YB. Mlombe - Chairperson (COMREC) Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an interim report in the course of the study and an end of study report.

4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 03-Jul-19. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

PHARMACY, MEDICINES & POISONS BOARD

Mission: To promote and improve the health of the population of Malawi through the regulation of Pharmacy Personnel, Pharmacy Businesses, Medicines and Allied Substances

ALL CORRESPONDENCE SHOULD BE ADDRESSED TO THE REGISTRAR

Head Office:
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LILONGWE 3, MALAWI

Phone: (+265) 01 755 165
Fax : (+265) 01 755 204
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Web: www.pmpb.mw

PMPB/CTRC/III/14062018102
DATE: 4th July, 2018

Department of Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine
Keppel St
London

Attn.: Dr. Titus Divala

RE: ACCURACY AND CONSEQUENCES OF USING TRIAL-OF-ANTIBIOTICS FOR TB DIAGNOSIS (ACT-TB STUDY).

Refer to your application to register the above mentioned clinical trial with the Pharmacy, Medicines and Poisons Board (PMPB).

The Clinical Trial Review Committee (CTRC), at its meeting held on 22nd June, 2018, issued a **No Objection** to the implementation of the trial after members agreed that the nature of the trial was seen to be outside the scope of trials that should be regulated by PMPB through the CTRC.

Please contact the undersigned if there are any issues that need further clarification.

Yours faithfully,

M. Kawaye
ACTING REGISTRAR

PHARMACY MEDICINES & POISONS BOARD
REGISTRAR
04 JUL 2018
P.O. BOX 30241, LILONGWE 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			06.11.2018	2018/1964/REK nord
			Deres dato:	Deres referanse:
			25.09.2018	

Vår referanse må oppgis ved alle henvendelser

Jon Øyvind Odland
Institutt for samfunnsmedisin

2018/1964 En kontrollert klinisk studie for å undersøke responsen til bredspekret antibiotika som en eksklusjonsdiagnose i allmenpraksis mot risiko for antibiotika resistens

Forskningsansvarlig institusjon: UiT Norges arktiske universitet
Prosjektleder: Jon Øyvind Odland

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 25.10.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hforskn) § 10.

Prosjektleders prosjektomtale
Det skal undersøkes, ved hjelp av en randomisert, kontrollert studie om respons til bredspekret antibiotika kan brukes som eksklusjonsdiagnose for tuberkulose. Dette skal vurderes opp mot risiko for resistensutvikling knyttet til behandingen. Tre grupper (625 per gruppe) individuelt randomisert (1:1:1), med åpen informasjon undersøkes med standard diagnostisk tilnærming. Kun voksne deltakere, med full brukermedvirkning og informert samtykke. Studien kan forenkle dignostikk og klinikk for en utsatt gruppe mennesker. Studien skal i sin helhet foregå i Malawi. Alle etiske godkjenninger fra Malawi og London er vedlagt.

Komiteen vurderte at Hanne Husom Haukland var inhabil og hun fratrådte møtet da saken ble behandlet, jf. fvl. § 6.

Om prosjektet
Prosjektet er en del av en PhD. Studenten skal avlegge sin PhD i London.

Dette er et samarbeidsprosjekt mellom Universitetet i Malawi, London School of Hygiene and Tropical Medicine, og Universitetet i Tromsø.

Prosjektet skal gjennomføres i Malawi og er et «Tuberkulose initiativ» fra Helse Nord.

Det foreligger godkjenning fra London School of Hygiene and Tropical Medicine, og University of Malawi.

Data
Det skal hentes data fra pasientjournal og fra lokale poliklinikker. Data er standard medisinske opplysninger knyttet til infeksjoner og sykehistorie.

Nye helseopplysninger er respons på behandling av infeksjoner.

Data avidentifiseres med koblingsnøkkel. Database oppbevares i 5 år i Malawi.

Deltakere/rekruttering
Voksne deltakere fordeles i tre grupper voksne deltakere (625 per gruppe), individuelt randomisert. Deltakere rekrutteres gjennom behandling på poliklinikkene.

REK har ingen innvendinger til prosjektet

Vedtak
REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider og godkjenner det med hjemmel i helseforskningsloven § 10. REK forutsetter at prosjektet også har godkjenning fra Malawi.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 21.03.2022, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:jon.oyvind.odland@uit.no

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

9 May 2018

Dear Titus ,

Study Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

LSHTM ethics ref: 15232

Thank you for your application for the above research, which has now been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Safety Information	ACT_PackageInsertAzithromycin	14/03/2013	JUNE 2013
Safety Information	ACT_PackageInsertAmoxicillin	21/12/2015	DEC 2015
Sponsor Letter	2018-KEP-077_Sponsor Confirmation_13.03.18	13/03/2018	1
Other	GCP Cert_LSHTM_TDivala_21.03.18	21/03/2018	1
Investigator CV	ACT-CV1_TitusDivala	30/03/2018	1
Investigator CV	ACT-CV2_KatherineFielding	30/03/2018	1
Investigator CV	ACT-CV3_LizCorbett	30/03/2018	1
Information Sheet	ACT-20180330InformedConsentEnglish	30/03/2018	1.0
Information Sheet	ACT-20180330InformedConsentChichewa	30/03/2018	1.0
Protocol / Proposal	ACT-20180330Protocol	30/03/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

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Improving health worldwide

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Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

12/04/2019

Dear Titus,

Project Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

Project ID: 15232

Thank you for your annual report application for the continuation of your research dated 09/04/2019 12:01 , which has now been considered by the Chair on behalf of the Ethics Committee.

Confirmation of ethical opinion

This application is approved by the committee for a further year.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

After ethical review

Any changes to the application must be submitted to the committee via an Amendment form.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reaction (SUSARs) which occur during the project by submitting a SUSAR and Protocol Violation form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor John DH Porter
Chair

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Improving health worldwide

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	27
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	19

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	19
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community	8

		clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event),	10

		method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any	14

		planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any	14

		related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis	#20c	Definition of analysis population relating to	18

population and missing data		protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p28, appendix (protocol)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p28, appendix (protocol)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p28, appendix (protocol)
Ethics and			

dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p28 appendix (consent)
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	p28 appendix (consent)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p28 appendix (consent)
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements	p28, appendix (protocol)

		that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p28, appendix (protocol)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	p28, appendix (protocol)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	p28, appendix (protocol)
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	p28 appendix (consent)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for	p28 appendix (consent/protocol)

future use in ancillary studies, if applicable

Notes:

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BMJ Open

Accuracy and Consequences of using Trial-of-antibiotics for TB diagnosis (ACT-TB Study): protocol for a randomised controlled clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033999.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Jan-2020
Complete List of Authors:	Divala, Titus; London School of Hygiene and Tropical Medicine, TB Centre; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative Fielding, Katherine; London School of Hygiene & Tropical Medicine, TB Centre; University of the Witwatersrand, School of Public Health Sloan, Derek; University of Saint Andrews, School of Medicine French, Neil; University of Liverpool Faculty of Health and Life Sciences, Centre for Global Vaccine Research, Institute of Infection and Global Health Nliwasa, Marriott; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; London School of Hygiene and Tropical Medicine, TB Centre MacPherson, Peter ; Liverpool School of Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme Kandulu, Chikondi; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; Malawi Liverpool Wellcome Trust Clinical Research Programme Chiume, Lingstone ; Malawi Liverpool Wellcome Trust Clinical Research Programme; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative Chilanga, Sanderson ; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; Malawi Liverpool Wellcome Trust Clinical Research Programme Ndaferankhande, Masiye; Malawi Liverpool Wellcome Trust Clinical Research Programme Corbett, Elizabeth ; London School of Hygiene and Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Diagnostics, Epidemiology, Evidence based practice, General practice / Family practice, HIV/AIDS
Keywords:	trial-of-antibiotics, Tuberculosis < INFECTIOUS DISEASES, TB, antimicrobial resistance, diagnostic performance, antibiotics

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TITLE

Accuracy and Consequences of using *Trial-of-antibiotics* for TB diagnosis (ACT-TB Study): protocol for a randomised controlled clinical trial

Authors

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KEY WORDS

trial-of-antibiotics, tuberculosis, TB, antimicrobial resistance, AMR, antibiotics, diagnostic performance, sensitivity, specificity, randomised controlled clinical trial, randomised, RCT

Protocol version 3.0, 19 Feb 2019

ABSTRACT:

Introduction

Over 40% of global tuberculosis case notifications are diagnosed clinically without mycobacteriological confirmation. Standard diagnostic algorithms include "trial-of-antibiotics" –empirical antibiotic treatment given to mycobacteriology-negative individuals to treat infectious causes of symptoms other than tuberculosis, as a "rule-out" diagnostic test for tuberculosis. Potentially 26.5 million such antibiotic courses/year are prescribed globally for the 5.3 million/year mycobacteriology-negative patients, making trial-of-antibiotics the most common tuberculosis diagnostic, and a global-scale risk for antimicrobial resistance (AMR). Our systematic review found no randomised controlled trial (RCT) to support use of trial-of-antibiotic. The RCT aims to determine the diagnostic and clinical value and AMR consequences of trial-of-antibiotics.

Methods and analysis

A three-arm, open-label, RCT randomising (1:1:1) Malawian adults (≥18years) seeking primary care for cough into: a) azithromycin 500mg once daily for 3 days, or b)amoxicillin 1g three times/day for 5 days, or c) standard-of-care (no immediate antibiotic). We will perform Mycobacteriology tests (microscopy, Xpert/MTB/RIF and Mycobacterium-Tuberculosis culture) at baseline. We will use Audio-Computer-Assisted-Self-Interview (ACASI) to assess clinical improvement at day eight. First primary outcome will be proportion of patients reporting day-eight improvement out of those with negative mycobacteriology (specificity). Second primary outcome will be day 29 incidence of a composite endpoint of either death or; hospitalisation or; missed tuberculosis diagnosis. To determine AMR impact we compare proportion of resistant nasopharyngeal *Streptococcus pneumoniaee* isolates on day 29. 400 mycobacteriology-negative participants/arm will be required to detect a ≥10% absolute

difference in diagnostic specificity with 80% power. We will estimate measures of effect by comparing outcomes in antibiotic arms (combined and individually) to standard-of-care.

Ethics and dissemination

The study has been reviewed and approved by Malawi College of Medicine Research and Ethics Committee, London School of Hygiene &Tropical Medicine (LSHTM) Research Ethics Committee, and Regional Committee for Health and Research Ethics –Norway, and Malawi Pharmacy, Medicines, and Poisons Board (Appendix 1). We will present abstracts at relevant conferences, and prepare a manuscript for publication in a peer-reviewed journal.

Registration

Clinicaltrials.gov, NCT03545373

Strengths and limitations

- To our knowledge this is the first randomised controlled trial to address benefits and consequences of using antibiotics as an exclusion diagnostic for tuberculosis, a widely used practice that results in millions of antibiotic prescriptions/year.
- We will also contribute evidence on AMR affecting common antimicrobials used for managing respiratory infections.
- The use of ACASI for assessing clinical response and adherence to antibiotic treatment which can be used in future studies.
- Acknowledged weaknesses include limited power to evaluate safety of deferred antibiotic treatment; conduct subgroup analysis by HIV status; and the possibility that participants randomised to the standard-of-care arm may find alternative access to antibiotics therefore misclassifying exposure/intervention status.

INTRODUCTION

The high case-fatality rate for tuberculosis, the leading global infectious cause of death in adults[1] with approximately 10 million cases and 1.6 million deaths in 2017,[2] in part reflects suboptimal diagnostics.[3-6] To complement this diagnostic gap, standard algorithms throughout the world include a “trial-of-antibiotics” (Figure 1). This is a course of broad-spectrum antibiotics, with negligible *Mycobacterium tuberculosis* activity, given to patients with symptoms such as cough in order to “rule-out” or “rule in” tuberculosis.[7-9] In clinical practice and most national guidelines (summarised in figure 1), patients who have negative sputum mycobacteriology and have responded to antibiotic treatment are considered tuberculosis-negative while those who remain symptomatic are deemed likely to have tuberculosis and undergo further evaluations potentially leading on to receiving tuberculosis treatment.[7-9]

We estimate that 26.5 million courses of antibiotics are prescribed in the diagnosis of the 5.3 million smear negative tuberculosis registrations recorded annually,[10] making antibiotics the most common diagnostic for tuberculosis.[11] Our 26.5 million estimate assumes that for every one smear-negative tuberculosis case detected, five antibiotics courses are used: the first two courses being given to patients are ultimately registered as smear-negative tuberculosis, while the other three courses represent patients whose symptoms resolved without starting anti-tuberculosis treatment.[4 12] This high frequency of prescription of important broad-spectrum antibiotics raises a global-scale risk for antimicrobial resistance (AMR) which like tuberculosis, is a major crisis, becoming in 2016 one of only four health topics ever to be discussed at the United Nations General Assembly.[13-16]

We performed a systematic literature review[17] which demonstrated that, despite being in global and national guidelines for decades, trial-of-antibiotics has a limited supporting evidence base but with the available evidence suggesting poor diagnostic performance.[18] None of the identified studies was an RCT and most of the observational studies were very small and not primarily designed to assess the benefits and consequences of trial-of-antibiotics. Pooled sensitivity and specificity of trial-of-antibiotics versus mycobacteriology tests were below internationally defined minimum performance profiles for tuberculosis diagnostics.[19]

We hypothesise that use of antibiotics in the course of evaluating patients for tuberculosis has both benefits and risks that need to be weighed carefully to optimise patient and public health outcomes. We will address evidence gaps related to a) accuracy, b) antimicrobial resistance, and c) impact on clinical outcomes of trial-of-antibiotics by conducting an RCT (ACT-TB Study) recruiting adult patients with cough presenting to health centres in Blantyre, Malawi. To our knowledge this is the first randomised controlled trial to rigorously address these questions.

METHODS AND ANALYSIS

Study design

This is a three-arm individually randomised (1:1:1), open-label controlled clinical trial (RCT) investigating accuracy and broader clinical, and antimicrobial resistance impact of using trial-of-antibiotics to rule-out tuberculosis among adults presenting with cough at primary care centres in Malawi (Figure 2). The trial is registered with Clinicaltrials.gov (NCT03545373) (Appendix 2). The full trial protocol is provided as Appendix 3.

Study setting

We will screen adults aged at least 18 years presenting to Limbe and Ndirande health centres in Blantyre, Malawi. Blantyre has an estimated tuberculosis prevalence of 1,014 per 100,000 (95% CI: 486 to 1,542), and an estimated adult HIV prevalence of 12.7% (95% CI: 11.9 to 13.6).[20]

Eligibility criteria

We will offer enrolment to patients who satisfy the following inclusion and exclusion criteria.

Inclusion Criteria

- Ambulatory clinic attendees presenting with cough
- Unwell for at least 14 days
- Aged at least 18 years
- Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period.

Exclusion Criteria

- Self-reported allergy to study medications

- WHO/Malawi National tuberculosis Program (NTP) danger signs: respiratory rate > 30/min, temperature >39^{o}C, Heart rate >120/minute, confused/agitated, respiratory distress, systolic blood pressure <90 mmHg, inability to walk unassisted
- Treated with antibiotics other than co-trimoxazole prophylaxis within the past 14 days
- Tuberculosis treatment or isoniazid preventive therapy within the last 6 months

Interventions

We will randomise participants, in a ratio of 1:1:1, to the following arms:

- **Arm 1** (Azithromycin): Azithromycin 500mg taken once daily for 3 days from enrolment day
- **Arm 2** (Amoxicillin): Amoxicillin 1g taken three times daily for 5 days from enrolment day.
- **Arm 3** (Standard of care): No study antibiotic prescription.

Rationale for interventions

Amoxicillin was chosen because it is the standard antibiotic used as first line treatment and for trial-of-antibiotics in Malawi. However, amoxicillin may not demonstrate the best performance for trial-of-antibiotics because of increasing resistance, and a narrow coverage for aetiology of community acquired pneumonia and “atypical” organisms. We chose azithromycin to represent the optimal biological specificity of an oral regimen due to more complete coverage of atypical organisms that cause community acquired pneumonia (e.g mycoplasma and chlamydia), and also the low resistance rates in Malawi where macrolides are rarely used. The dose for Azithromycin is as recommended in the British National Formulary (BNF) as treatment for community acquired pneumonia.[21] The dose for amoxicillin is the BNF recommendation for severe infections but it is the recommended first line established by the Department of Medicine at Queen Elizabeth Central Hospital (Blantyre, Malawi) based on local microbiology.

Timing of interventions

The standard of care in Malawi defined by National Tuberculosis Programme guidelines for primary care patients presenting with cough who are otherwise well (no danger signs) is to take two sputum specimens for smear microscopy or Xpert and ask patients to return for

results, typically 3 days - 1 week later (Figure 1). The Malawi tuberculosis diagnostic algorithm recommends use of broad-spectrum antibiotics as trial-of-antibiotics after negative sputum tests are provided to patients who remain symptomatic. Therefore, the ideal population for randomisation for this study are patients on who already have negative results for smear microscopy or Xpert. However, that may have ethical challenges considering the implications of withholding treatment (if randomised to reference arm) from a symptomatic patient who, according to guidelines, should be given antibiotics. The first visit therefore was the most ideal time for randomisation and is in line with recommendations for test interval in investigations evaluating diagnostic tests with respect to the time interval between the index test (trial-of-antibiotics) and the reference test (mycobacteriology sputum sample collection). The timing also conforms to common clinical practice of prescribing trial-of-antibiotics at the same time as sputum collection to reduce diagnostic delay. The design was discussed with the District Health Office and the national tuberculosis programme ahead of ethics submission.

Known drug reactions

Azithromycin and amoxicillin have a long registration history, have been widely used globally and are well tolerated. Rare side effects for azithromycin include nervousness, dermatologic reactions including Stevens–Johnson syndrome, anaphylaxis and prolonged QT interval. Rare side-effects for amoxicillin are mental state changes, light-headedness, photosensitivity and severe allergic reactions.

Concomitant medication and interaction with other therapies

We do not have any restrictions with respect to concomitant medications apart from those listed in the exclusion criteria. We expect some participants to be on HIV antiretroviral drugs and some to subsequently start tuberculosis therapy. Important interactions therefore would be those those between the product and HIV antiretroviral drugs. There is no moderate or

major interaction between either azithromycin or amoxicillin with the classes of HIV antiretroviral drugs currently used in Malawi.

Trial restrictions

We do not require participants to have any dietary restrictions. We will also accept co-administration with contraception. Azithromycin and amoxicillin are both considered safe in pregnancy, so we will include pregnant women should they be eligible.

Assessment of compliance

On Day-8, we will document self-reported compliance adherence of study products.

Withdraw of interventions

The investigator may also terminate a participant from study product if indicated by an adverse reaction. If a participant stops taking study product either voluntarily or by investigator decision, they will be encouraged to remain in follow up and their data will form part of intention to treat analyses.

Study outcomes

The clinical trial has two separately powered, and distinctly assessed primary outcomes, one for diagnostic evaluation (Primary outcome 1: Day 8) and the other for clinical impact (Primary outcome 2: Day 29) of the intervention. The following are descriptions of all study outcomes:

Primary outcome 1: Specificity of day 8 symptom change versus mycobacteriology

The investigational test is change in symptoms at Day 8 categorised as: improved or not improved (no change or worsened) in response to the question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?*

As with all self-rated outcomes, social desirability bias (tendency of participants to answer questions in a manner that will be viewed favourably by healthcare worker), and interviewer bias (interviewers' subconscious or conscious influencing subject response) may affect the outcome. To minimise these biases in evaluation of improvement of baseline symptoms the interview will be conducted using Audio Computer Assisted Self-Interview (ACASI), a platform that allows patients to report their health state in private and directly into a database via an audio questionnaire administered by a tablet. The lack of human-to-human interaction will minimize interviewer, ascertainment, and social desirability biases. Another concern with open-label design is placebo-effect favouring those randomised to antibiotics over the standard of care arm that is however not addressed in our design.

We developed, piloted, and optimised the ACASI questionnaire in the study target population and arrived at the question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?* Before proceeding to the self-interview, participants will be oriented using test questions until study staff are sure that they will be able to go through the interview on their own. We will term ACASI interview outcome as **ACASI-test-negative** if the participant reports improvement or **ACASI-test-positive** if the participant reports no change or worsening.

The mycobacteriology reference standard will be defined in participants with at least one valid sputum test result on days 1 and 8 as **sputum-test-positive** if there is at least one positive of smear microscopy, Xpert/MTB/RIF, or MTB culture; and as **sputum-test-negative** if none of the tests is positive. To minimise bias, the sputum tests will be performed by a high-quality research laboratory in the University of Malawi College of Medicine by staff with no access to participant treatment allocation information or symptom results.

The specificity of day 8 symptom change (the index test measured using ACASI) against mycobacteriology tests (reference test) is defined as: **proportion of sputum-test-negative who are ACASI-test-negative.**

Primary outcome 2: Clinical impact of trial-of-antibiotics

We will investigate the overall clinical impact of trial-of-antibiotics by comparing the day 29 risk of any of death, hospitalisation, and "missed tuberculosis" (untreated mycobacteriological or radiological tuberculosis). All these events can lead to mortality and are potential consequences of trial-of-antibiotics; therefore, grouping them as a composite endpoint appropriately represents the effect of the intervention because: 1) there are similarities in the importance of each of the components, 2) the components occur with similar frequencies in the patient population, and 3) the direction of effect is anticipated to be the same for all.[22]

The connection between trial-of-antibiotics and risk of hospitalisation and death assumes a protective effect of antibiotics. In patients presenting with chronic cough at primary care in high HIV prevalence settings, frequencies of mortality and hospitalization over a two months period are similar, ranging from 2 to 6%.[23]

We have included missed tuberculosis diagnosis in our composite clinical outcome because this too can lead to death. We are defining "missed tuberculosis" as participants who meet standard mycobacteriological and radiological tuberculosis definitions but are incorrectly classified as tuberculosis-negative and not yet on tuberculosis treatment by Day 29. Clinical, radiological, and microbiological evaluation for tuberculosis will be done at Day 8, Day 29, as well as day between these two for patients who report worsening symptoms.

Secondary outcome 1: impact of trial-of-antibiotics on antimicrobial resistance

We will use *Streptococcus pneumoniae* isolated from swabs of the nasopharynx as the indicator pathogen for AMR evaluation. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient window for investigating antimicrobial resistance. *Streptococcus pneumoniae* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper

respiratory tract, acquires resistance readily, and has well documented laboratory investigation procedures in place.[24]

We will define **AMR positive** as having nasopharyngeal isolates of *Streptococcus pneumoniae* that are resistant to any of the following commonly used antibiotics: ceftriaxone, amoxycillin, cefoxitin, azithromycin, and erythromycin as determined using disc diffusion technique; and **AMR negative** as either (1) not isolating any *Streptococcus pneumoniae* or (2) isolating any *Streptococcus pneumoniae* that is not resistant to any of the assessed antibiotics. For each arm, and at both baseline and day 29, we will report proportion of AMR positive participants. The study outcome will be the proportion of AMR positive participants at day 29.

Secondary outcome 2: diagnostic value of trial-of-antibiotics in all patients including those without a valid sputum result

The investigational test is as described for primary outcome 1. The mycobacteriology reference standard will be defined as sputum test positive if at least one positive of smear microscopy, Xpert/MTB/RIF, or MTB culture from samples collected on days 1 and 8. The reference test will be sputum-test-negative if none of the tests is positive and where there is no valid sputum test result available. The most likely reason for not having a valid sputum result will be inability to produce sputum, but other explanations will be: lost sample before laboratory analysis, an invalid laboratory reading, or contamination. We have opted to analyse this population because in symptomatic adults of the study setting, failure to produce sputum can be as high as 13%.[23]

Secondary outcome 3: Economic evaluation

The objective of the economic evaluation is to undertake a cost-utility analysis to estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other. We will systematically compare costs and consequences associated with the interventions. We will perform a within trial comparison of the three treatment arms to estimate the incremental

cost per quality-adjusted life year (QALY) gained for the azithromycin or amoxicillin arm in comparison to standard of care. Costs will be estimated from the Malawian Ministry of Health perspective. Health outcomes will be quantified in QALYs, estimated from participants' responses to the Chichewa version of the EQ-5D-3L, a Health quality of life (HRQoL) measure.[25 26] We will adopt a time horizon matching the length of participant follow-up to achieve the within trial evaluation.

Exploratory outcomes

Our exploratory analyses will be comparisons between the **azithromycin** and **amoxicillin** arms for all our primary and secondary outcomes.

Planned subgroup analyses

We will perform analysis of primary outcomes stratified by HIV status and by ART status as documented on enrolment day. This is important because the study site has high prevalence of HIV and associated bacterial infections which may be amenable to antibiotics used for trial-of-antibiotics.

Study procedures

Figure 2 and Table 1 presents the study time schedule including a summary of patient identification, baseline procedures and outcome ascertainment at day 8 and day 29 follow up visits.

Screening

Study staff will approach patients with symptoms of pulmonary tuberculosis (including cough of any duration, fever, weight loss, and night sweats) with information about the study and seek written informed consent (Appendix 4) from all patients who meet eligibility criteria. After consenting, a participant will be given a unique study identification number confirming enrolment.

Randomisation

Randomisation will be in the ratio 1:1:1 to the three arms of the trial, using block-randomisation with variable block sizes, and stratified by study site. An independent statistician will prepare the randomisation list using Ralloc command in Stata software, then print each allocation alongside a randomisation number, and seal in opaque envelopes. Upon confirming eligibility and consenting status a designated site staff will open the next available of sequentially numbered randomisation envelopes and administer the allocated study arm.

Blinding

The study is not placebo controlled because of funding limitations, and so will not use blinding due to the nature of the study design. However, study team masking will be maintained with all study outcome assessment occurring without reference to randomisation arm.

Baseline procedures

At baseline, we will collect demographic data, clinical history, record vital signs, height and weight. Participants will be requested to provide two sputum samples for Xpert/MTB/RIF and two more sputum samples the following morning for smear microscopy and MTB culture. We will also collect a urine sample for lipoarabamannan antigen detection (TB LAM); and a nasopharyngeal swab for pneumococcal culture and sensitivity testing. We will offer and perform HIV testing according to the national algorithm, and link all who test positive to care. To minimise loss to follow up, we will collect contact phone numbers, a physical address and geolocation information.

Participant follow up

On day 8, the first activity (ahead of any other interaction with study staff) will be the ACASI. Other activities include providing results for day 1 tuberculosis tests and linking those who test positive to care; collection of another sputum sample for smear microscopy and

Mycobacterium tuberculosis (MTB) culture; and management of ongoing symptoms and other illnesses. On visit day 29, the final study visit, we will document participant vital status, hospitalisations, and establish adherence to HIV and tuberculosis treatment. We will also collect nasopharyngeal swab samples from all participants, and sputum from those with tuberculosis symptoms.

Participant retention

To minimise loss to follow up, we will record geolocation information of participants' place of residence using ePAL android app, a high-resolution mapping system validated in Blantyre. We will also record up to 3 contact phone numbers of the participant and their nominated friends and relatives. We will not replace participants who discontinue study participation or study treatment regardless of reason for withdrawal or discontinuation or the time either of these occurs.

Data management

We will collect data using TeleForm (paper based system that uses optical character recognition) and Open Data Kit systems (ODK, an electronic data capture system installed on android devices). Data will be committed to a secure database located at Malawi-Liverpool Wellcome Trust (MLW) within 2 days for TeleForm, and 7 days for ODK.

368 **Table 1:** key study procedures over the study period

	STUDY PERIOD			
	Enrolment	Follow up		
TIMEPOINT	Day-1	Day-8		Day-29
ENROLMENT:				
Eligibility screen	x			
Informed consent	x			
Allocation	x			
INTERVENTIONS:				
Azithromycin	x			
Amoxicillin	x			
Standard of care	x			
ASSESSMENTS:				
Demographics	x			
History of antibiotic use	x	x		x
History & examination[1]	x	x		x
Sputum collection[2]	x	x		
Urine for TB LAM test[3]	x	x		
Nasopharyngeal swab for AMR[4]	x			x
HIV test	x			
Linking to routine care	x	x		x
ACASI[5]		x		
Clinical events[6]				x
Update contact & address		x		x

1. For symptomatic participants, Day-8 sputum mycobacteriology should be fast-tracked to inform care before they leave the clinic.
2. Give sputum bottles at end of Day-1 visit for submission on Day-8. Also collect sputum and perform mycobacteriology at any time of the study when clinically indicated
3. Urine Lipoarabinomannan for Tuberculosis Diagnosis (TB LAM)
4. Nasopharyngeal swab for Streptococcus pneumoniaeee culture and sensitivity as a way of determining risk of antimicrobial resistance (AMR)
5. Audio Computer Assisted Self-Interview (ACASI) for documenting change of symptoms on Day- 8 versus Day-1
6. Illnesses, clinic visits, radiological outcomes, new HIV diagnosis, new tuberculosis diagnosis, death, hospitalisation, missed tuberculosis diagnosis, HIV care loss to follow up, and tuberculosis care loss to follow up

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Statistical approach

We will summarise the processes of recruitment including non-eligibility and reasons of exclusion in a CONSORT (Consolidated Standards of Reporting Trials) flow chart. We will describe the study participants by their baseline characteristics, by arm. We will perform analyses of all our outcomes based on an intention to treat analysis (using the arm patient was randomised to). Analysis for primary outcome 1 will be restricted to participants with a valid sputum test result. We will report measures of effect from the following comparisons:

i) Azithromycin or amoxicillin (combined) versus standard of care

ii) azithromycin versus standard of care

iii) amoxicillin versus standard of care

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for study site. For each comparison, we will report 95% confidence intervals (CIs) and p-values from the likelihood test. If outcomes are rare, or the GLM model does not converge, we will use logistic regression to estimate the treatment effect using an odds ratio. We will report the odds ratios with their associated 95% CIs and p-values.

We will perform data cleaning and analysis using Stata release 15 (Stata Corp, College station, Texas, USA). The statistical approach will be expanded in a detailed statistical analysis plan, which will be finalised before unblinding the study data.

Sample size and power

We performed power and sample size estimations for the diagnostic impact, clinical impact, and AMR impact outcomes as described below. Our sample size estimations are based on planned analysis that will use Chi-squared test for comparing two independent proportions. We applied a normal-approximation correction for continuity.

Diagnostic impact outcome

We assume that at Day 8, change in well-being from baseline state in trial-of-antibiotics (azithromycin or amoxicillin) arms will correctly classify 60% of all mycobacteriology negative participants (i.e 60%specificity of day 8 symptom change in trial-of-antibiotics arms). [12] We wanted to estimate a sample size that would provide a discriminatory power of 80% at a two-sided significance level of 5%, to detect at least 10% difference in specificity (i.e ≤50% specificity of day 8 symptom change in standard of care arm). The sample sizes will differ by the number of arms being compared, we have therefore provided two separate estimates in line with type of comparisons specified under section 7.

Sample size for a combination of 2 antibiotic arms against standard of care arm

The sample size estimates along with assumptions for this comparison are shown in the Table 2A. To achieve the desired 80% discriminatory power, we will need to recruit at least 305 sputum-test-negative participants per arm. Accounting for TB prevalence, ability to produce and submit sputum, and loss-to-follow up increases the sample to 472 per arm or 1,416 for the whole study.

Table 2A: Sample size estimation for the *diagnostic impact outcome* comparing a combination of two antibiotic arms to standard of care arm

POWER (X2 difference between independent proportions**)**	**Effect size (**50% SoC vs 60% amoxycillin or azithromycin**)**	**Effective sample per arm (**Sputum negative participants needed**)**
0.70	0.10	325
0.75	0.10	363
0.80	0.10	400
0.85	0.10	463
0.90	0.10	538

Target power and respective sample size estimates based on knowledge of TB risk, ability to produce and submit sputum, and loss-to-follow up.

Sample size for one antibiotic arm against standard of care arm

The sample size estimates along with assumptions for this comparison are shown in the Table 2B. To achieve the desired 80% discriminatory power, we will need to recruit at least 400 sputum-test-negative participants per arm. Accounting for TB prevalence, ability to produce and submit sputum, and loss-to-follow up increases the sample to 625 per arm or 1,875 for the whole study.

Table 2B: Sample size estimation for the *diagnostic impact outcome* one antibiotic arm to standard of care arm

POWER (X2 difference between independent proportions**)**	**Effect size (**50% SoC vs 60% amoxycillin or azithromycin**)**	**Effective sample per arm (**Sputum negative participants needed**)**
0.70	0.10	243
0.75	0.10	271
[redacted]	[redacted]	[redacted]
0.85	0.10	347
0.90	0.10	403

[redacted] Target power and respective sample size estimates based on knowledge of TB risk, ability to produce and submit sputum, and loss-to-follow up.

Power for clinical impact outcome

For the clinical impact of trial-of-antibiotics outcome, we assume a 4% baseline risk of composite outcome, and a loss to follow up of 10% by Day 29. Using the sample size of 625 participants per arm (obtained in Table 2B), and a type I alpha of 5%, we will be able to detect the difference between arms with 80% power, if the risk in the intervention arm is twice that of the standard of care arm. This estimate is applicable to all comparisons shown in section 3.

Power for AMR outcome

Study arms will be compared based proportion of participants with resistant *Streptococcus pneumoniae* on day 29. We assume that 45% of Day-29 nasopharyngeal swabs will successfully grow *Streptococcus pneumoniae,* and that 10% of the isolates will meet the definition of resistance (described earlier under outcomes), and that 10% will be lost to follow up by Day 29. Therefore, on day 29, the standard of care arm (of 625 participants) will have 253 *Streptococcus pneumoniae* isolates, 25 of which would meet the definition of resistance. This translates into a 4% (25/625) risk of AMR positive cases in the standard of care arm. To detect a twofold change in odds of day 29 AMR risk with at least 80% power, using Pearson's Chi-squared test, at 0.05 alpha, we will need at least 431 and 553 participants per arm for the 2:1 and pairwise comparisons respectively.

Monitoring and oversight

The trial will be monitored by the Research Support Centre Clinical Trials Unit of the University of Malawi College of Medicine. An independent Data and Safety Monitoring Board (DSMB), and a Trial Steering Committee (TSC) have been set up and meet bi-annually.

Trial closure

We will consider the trial closed after completing follow up of the last enrolled participant, and upon recording all mycobacteriology laboratory reports. Antimicrobial resistance lab work will continue beyond trial closure. The trial may be terminated early by the trial steering committee upon recommendation of the DSMB. The halting rule for a trial arm is an unacceptable high level of deaths assessed using an alpha determined at the first DSMB meeting.

PATIENT AND PUBLIC INVOLVEMENT

Patients were involved in the design of the study especially the audio-computer-assisted interview (ACASI) used for collecting primary outcome data. Health workers were involved in the design of study visits and patient flow.

DISCUSSION

The ACT-TB study will investigate the benefits and consequences of "trial-of-antibiotics," a widely promoted approach to many patients with suspected tuberculosis in low- and middle-income countries without solid evidence base. To our knowledge, ACT-TB Study is the first RCT of this kind. Results of our trial will add to the evidence-base regarding routine diagnosis of tuberculosis in low and middle-income countries and strengthen our fight against AMR. Both tuberculosis and AMR are diseases of major importance globally, with tuberculosis causing an estimated 1.6 million deaths in 2017 and AMR projected to cause 10 million deaths per year by 2050.[2 27]

Choice of study interventions

We have chosen amoxicillin because it is the first line treatment for outpatient management of pneumonia in Malawi and is commonly used for trial-of-antibiotics. It also provides data of immediate programmatic relevance and a starting point to investigate exacerbation of pre-existing AMR pressure. However, amoxicillin may not demonstrate the full benefits for trial-of-antibiotics because of organisms with intrinsic ("atypicals") or acquired (common in gram-negative organisms, and *Staphylococcus aureus*) penicillin resistance.[28] Oral antibiotics that may provide the better diagnostic discrimination for bacterial versus mycobacterial causes of cough are macrolides, such as azithromycin, because of better intrinsic coverage of "atypical" intracellular organisms such as *mycoplasma* species that cause community acquired pneumonia,[29-31] and low levels of acquired macrolide-resistance in bacterial isolates in Malawi.[28]

ACASI for post-treatment improvement assessment

Our systematic review[18] did not identify a consistent definition of tuberculosis or no tuberculosis based on trial-of-antibiotics. A definition of clinical change following antibiotic treatment is necessary for the trial-of-antibiotics as this determines who get categorised as well or tuberculosis-positive. Approaches that ranged from self-reported improvement to a combination of clinical and radiological assessments are likely to be highly subjective and prone to bias, as well as being a potentially avoidable source of heterogeneity between studies. In this study, we hope to address these biases (particularly, inter-observer variability, and patient/interviewer reporting or ascertainment biases) by using self-rated change of illness (on day 8) recorded using a self-completed questionnaire, the ACASI (described under outcomes). The ACASI questionnaire, the delivery platform, and the resulting data management can all be replicated in future studies, creating potential for more standardisation in assessment of clinical response to treatment.

Potential clinical impact of antibiotics

In areas with high HIV prevalence, empirical antibiotics during tuberculosis investigations could be life-saving: mortality immediately before and after tuberculosis diagnosis is high, [3 32] and is often secondary to severe bacterial infections.[32-34] The leading aetiologies of infection and death on tuberculosis treatment as well as among outpatients with tuberculosis-like symptoms are *Streptococcus pneumoniaee* and non-typhoidal salmonellae: both can present with cough (primary cause) or as co-morbidities (super-infections) in patients presenting with active *Mycobacterium tuberculosis* disease.[32-34] If effective treatment of this type of life-threatening primary/super-infections reduces mortality during the diagnostic work-up of suspected tuberculosis in people living with HIV, then empirical use of broad-spectrum antibiotics would be indicated for this purpose alone, irrespective of any diagnostic contribution to tuberculosis treatment decisions. In this context, azithromycin may be the

most effective arm, as salmonella infections are highly sensitive to azithromycin, but not to amoxicillin.[28]

AMR and trial-of-antibiotics

Antimicrobial resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been investigated before. Previous work has shown that empirical antibiotics can drive rapid emergence of antimicrobial resistance.[35 36] Co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010[37]. Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniaee*, but with increased macrolide-resistance 6 months later.[38 39]

In this study we have the opportunity to assess the extent to which brief exposure drives antimicrobial resistance during diagnostic work-up for tuberculosis. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient sampling opportunity for investigating antimicrobial resistance.[40] *Streptococcus pneumoniae* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract, acquires resistance readily, and has well documented laboratory investigation procedures in place.[24] As exploratory analyses, we will also assess nasopharygeal colonization and antimicrobial resistance in relation to tuberculosis treatment and HIV status.

Important subgroups

Clinical response to trial-of-antibiotics is possible and indeed well-described in patients with bacteriologically confirmed tuberculosis (i.e. false-negatives/low sensitivity from the perspective of tuberculosis diagnosis) may relate to multiple super-infections.[4 33] As such, this phenomenon may vary by HIV status, since multiple concurrent infections are a hallmark of advanced HIV immunosuppression, and are most commonly reported in patients with

suspected tuberculosis in the pre-ART era. In 2015, in Malawi, 45% of adults who presented to primary care with prolonged cough (≥2 weeks) were HIV-positive, of whom only ~20% started tuberculosis treatment on the basis of positive mycobacteriology.[23] As such, the benefits and consequences of trial-of-antibiotics may vary by HIV status and ART coverage, and by subsequent tuberculosis treatment decisions. We will, therefore, include a pre-specified sub-analysis of trial outcomes stratified by HIV and ART status.

Limitations

The study has several limitations. Firstly, we did not use a placebo-control arm. Secondly, the study is not adequately powered to evaluate safety of deferred antibiotic treatment or conduct subgroup analyses of outcomes by HIV status, both which are important evidence gaps. Other limitations include the possibility that participants randomised to the standard-of-care arm may find alternative access to antibiotics therefore misclassifying exposure/intervention status. There is also a possibility of misclassifying active tuberculosis status because of the suboptimal nature of the available tests.

ETHICS AND DISSEMINATION

The study has been reviewed and approved by the University of Malawi College of Medicine Research and Ethics Committee (COMREC; registration number P.04/18/2381), the London School of Hygiene & Tropical Medicine Research Ethics Committee (LSHTM EC; registration number 15232), and Regional Committee for Health and Research Ethics, NTNU-Midt, Norway (REK nord; registration number 208/1964). Regulatory approval has been granted by the Malawi Pharmacy, Medicines, and Poisons Board (PMPB; registration number CTRC/III/14062018102). We will present any future protocol modifications to these bodies before implementing. We will submit results for publication in a peer-reviewed journal. We will submit abstracts to relevant national and international conferences. This work will also

form part of a PhD thesis for TD, which he will submit to the LSHTM. This study will follow the standards set by CONSORT guidelines.

AUTHORS' CONTRIBUTIONS

THD, KF and ELC are the main contributors to the conception, and design of the study. DS, MN and PM contributed to the general study planning and clinical design. NF contributed to the general study planning and antimicrobial resistance design. CK, LC, SC, and MF contributed to the design, piloting, and refining of study and clinical procedures. THD developed the first draft of the manuscript. All authors carefully reviewed and substantially contributed to the development of the trial protocol and this manuscript. All authors read and approved the final manuscript. THD is the guarantor for this work.

FUNDING AND SPONSORSHIP STATEMENT

The clinical trial is funded by the Commonwealth Scholarship Commission and the Helse Nord RHF grant awarded to THD. This work is part of THD's PhD work at London School of Hygiene & Tropical Medicine (LSHTM). LSHTM is the sponsor of this clinical trial (sponsor address: Keppel Street, Bloomsbury, London WC1E 7HT). ELC is funded by a Wellcome Trust Senior Research Fellowship in Clinical Science: WT200901. The funding agencies and the sponsor had no role in the preparation of the protocol or the intention to submit this manuscript for publication.

COMPETING INTERESTS STATEMENT

We have no conflicts of interest to declare.

BODY WORD COUNT: 4,034

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LEGENDS FOR FIGURES

1. Legend for figure 1

*The common clinical practice is that outpatients start antibiotics at the time of submitting sputum, to avoid the need for a third clinic visit to complete the algorithm.

Figure 1: The position of trial-of-antibiotics in standard algorithms for diagnosis of tuberculosis in low and middle income countries (based on the 2018 WHO GLI model guidelines and as implemented in national guidelines e.g Ghana, Malawi and South Africa.)

2. Legend for figure 2

ART = antiretroviral treatment for HIV

NTP = Malawi National Tuberculosis Program

TB LAM = Urine Lipoarabinomannan for Tuberculosis Diagnosis

VL = HIV Viral load

Figure 2: Flow diagram for the clinical trial in Blantyre, Malawi

3. Legend for figure 3

Figure 3: Assessing the diagnostic value of a change in symptoms from baseline to day 8

APPENDIX 1: ETHICS AND REGULATORY APPROVALS

(attached separately)

APPENDIX 2: TRIAL REGISTRATION—DATA SET

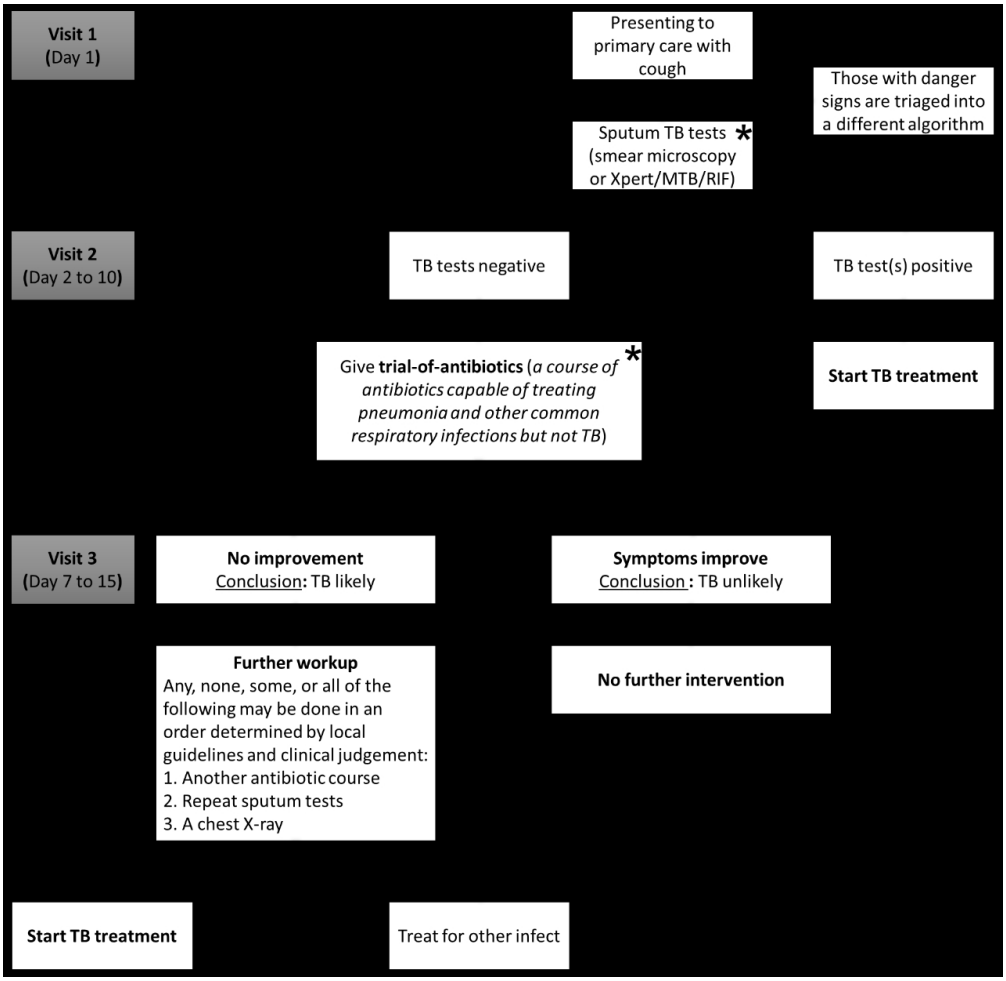
(attached separately)

APPENDIX 3: FULL TRIAL PROTOCOL

(attached separately)

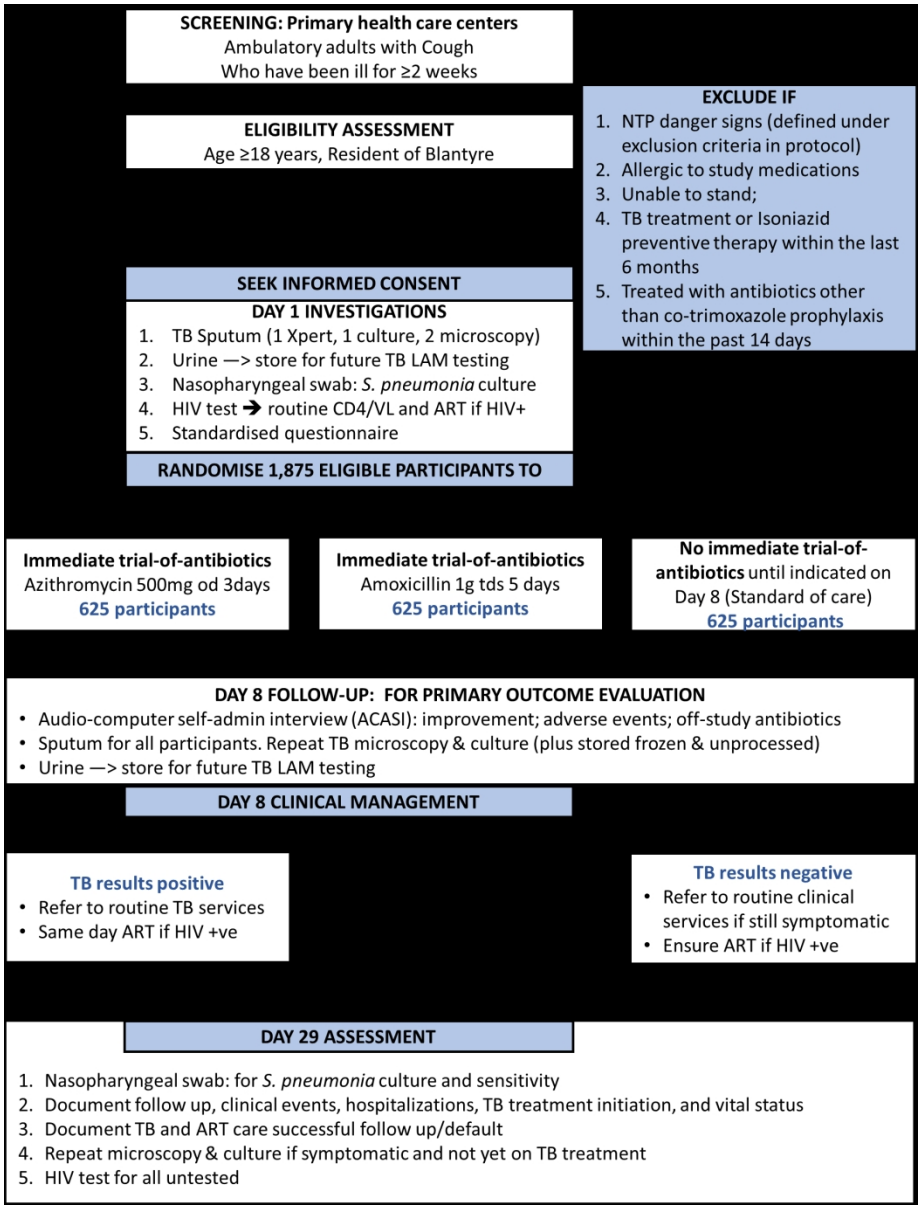
APPENDIX 4:PATIENT INFORMATION SHEET AND INFORMED CONSENT

(attached separately)



*The common clinical practice is that outpatients start antibiotics at the time of submitting sputum, to avoid the need for a third clinic visit to complete the algorithm.

Figure 1: The position of trial-of-antibiotics in standard algorithms for diagnosis of tuberculosis in low and middle income countries (based on the 2018 WHO GLI model guidelines and as implemented in national guidelines e.g Ghana, Malawi and South Africa.)



ART = antiretroviral treatment for HIV
NTP = Malawi National Tuberculosis Program
TB LAM = Urine Lipoarabinomannan for Tuberculosis Diagnosis
VL = HIV Viral load

Figure 2: Flow diagram for the clinical trial in Blantyre, Malawi

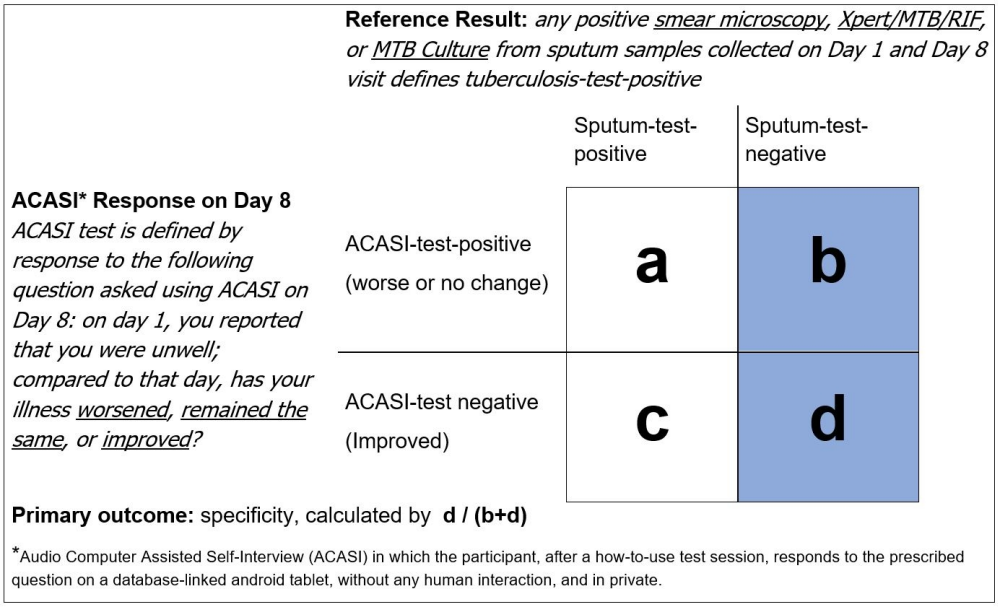


Figure 3: Assessing the diagnostic value of a change in symptoms from baseline to day 8

366x222mm (96 x 96 DPI)

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.04/18/2381 - Accurancy and Consequences of using Trial-of-antibiotics for TB diagnosis (ACT-TB Study) by Titus H Divala

On 03-Jul-18

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

Mlombe 03-Jul-18

Dr. YB. Mlombe - Chairperson (COMREC) Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an interim report in the course of the study and an end of study report.

4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 03-Jul-19. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

PHARMACY, MEDICINES & POISONS BOARD

Mission: To promote and improve the health of the population of Malawi through the regulation of Pharmacy Personnel, Pharmacy Businesses, Medicines and Allied Substances

ALL CORRESPONDENCE SHOULD BE ADDRESSED TO THE REGISTRAR

Head Office:
Off Paul Kagame/
Chilambula Road
P.O.Box 30241
Capital City
LILONGWE 3, MALAWI

Phone: (+265) 01 755 165
Fax : (+265) 01 755 204
Email: info@pmpb.mw
Web: www.pmpb.mw

PMPB/CTRC/III/14062018102
DATE: 4th July, 2018

Department of Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine
Keppel St
London

Attn.: Dr. Titus Divala

RE: ACCURACY AND CONSEQUENCES OF USING TRIAL-OF-ANTIBIOTICS FOR TB DIAGNOSIS (ACT-TB STUDY).

Refer to your application to register the above mentioned clinical trial with the Pharmacy, Medicines and Poisons Board (PMPB).

The Clinical Trial Review Committee (CTRC), at its meeting held on 22nd June, 2018, issued a **No Objection** to the implementation of the trial after members agreed that the nature of the trial was seen to be outside the scope of trials that should be regulated by PMPB through the CTRC.

Please contact the undersigned if there are any issues that need further clarification.

Yours faithfully,

M. Kawaye
ACTING REGISTRAR

PHARMACY MEDICINES & POISONS BOARD
REGISTRAR
04 JUL 2018
P.O. BOX 30241, LILONGWE 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			06.11.2018	2018/1964/REK nord
			Deres dato:	Deres referanse:
			25.09.2018	

Vår referanse må oppgis ved alle henvendelser

Jon Øyvind Odland
Institutt for samfunnsmedisin

2018/1964 En kontrollert klinisk studie for å undersøke responsen til bredspekret antibiotika som en eksklusjonsdiagnose i allmenpraksis mot risiko for antibiotika resistens

Forskningsansvarlig institusjon: UiT Norges arktiske universitet
Prosjektleder: Jon Øyvind Odland

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 25.10.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hforskn) § 10.

Prosjektleders prosjektomtale
Det skal undersøkes, ved hjelp av en randomisert, kontrollert studie om respons til bredspekret antibiotika kan brukes som eksklusjonsdiagnose for tuberkulose. Dette skal vurderes opp mot risiko for resistensutvikling knyttet til behandingen. Tre grupper (625 per gruppe) individuelt randomisert (1:1:1), med åpen informasjon undersøkes med standard diagnostisk tilnærming. Kun voksne deltakere, med full brukermedvirkning og informert samtykke. Studien kan forenkle dignostikk og klinikk for en utsatt gruppe mennesker. Studien skal i sin helhet foregå i Malawi. Alle etiske godkjenninger fra Malawi og London er vedlagt.

Komiteen vurderte at Hanne Husom Haukland var inhabil og hun fratrådte møtet da saken ble behandlet, jf. fvl. § 6.

Om prosjektet
Prosjektet er en del av en PhD. Studenten skal avlegge sin PhD i London.

Dette er et samarbeidsprosjekt mellom Universitetet i Malawi, London School of Hygiene and Tropical Medicine, og Universitetet i Tromsø.

Prosjektet skal gjennomføres i Malawi og er et «Tuberkulose initiativ» fra Helse Nord.

Det foreligger godkjenning fra London School of Hygiene and Tropical Medicine, og University of Malawi.

Data
Det skal hentes data fra pasientjournal og fra lokale poliklinikker. Data er standard medisinske opplysninger knyttet til infeksjoner og sykehistorie.

Nye helseopplysninger er respons på behandling av infeksjoner.

Data avidentifiseres med koblingsnøkkel. Database oppbevares i 5 år i Malawi.

Deltakere/rekruttering
Voksne deltakere fordeles i tre grupper voksne deltakere (625 per gruppe), individuelt randomisert. Deltakere rekrutteres gjennom behandling på poliklinikkene.

REK har ingen innvendinger til prosjektet

Vedtak
REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider og godkjenner det med hjemmel i helseforskningsloven § 10. REK forutsetter at prosjektet også har godkjenning fra Malawi.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 21.03.2022, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:jon.oyvind.odland@uit.no

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

9 May 2018

Dear Titus ,

Study Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

LSHTM ethics ref: 15232

Thank you for your application for the above research, which has now been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Safety Information	ACT_PackageInsertAzithromycin	14/03/2013	JUNE 2013
Safety Information	ACT_PackageInsertAmoxicillin	21/12/2015	DEC 2015
Sponsor Letter	2018-KEP-077_Sponsor Confirmation_13.03.18	13/03/2018	1
Other	GCP Cert_LSHTM_TDivala_21.03.18	21/03/2018	1
Investigator CV	ACT-CV1_TitusDivala	30/03/2018	1
Investigator CV	ACT-CV2_KatherineFielding	30/03/2018	1
Investigator CV	ACT-CV3_LizCorbett	30/03/2018	1
Information Sheet	ACT-20180330InformedConsentEnglish	30/03/2018	1.0
Information Sheet	ACT-20180330InformedConsentChichewa	30/03/2018	1.0
Protocol / Proposal	ACT-20180330Protocol	30/03/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

London School of Hygiene & Tropical Medicine
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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

12/04/2019

Dear Titus,

Project Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

Project ID: 15232

Thank you for your annual report application for the continuation of your research dated 09/04/2019 12:01 , which has now been considered by the Chair on behalf of the Ethics Committee.

Confirmation of ethical opinion

This application is approved by the committee for a further year.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

After ethical review

Any changes to the application must be submitted to the committee via an Amendment form.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reaction (SUSARs) which occur during the project by submitting a SUSAR and Protocol Violation form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

APPENDIX 1: TRIAL REGISTRATION—DATA SET

NCT Number	NCT03545373
Title	Accuracy and Consequences of Using Trial-of-antibiotics for TB Diagnosis (ACT-TB Study)
Acronym	ACT-TB
Status	Recruiting
Study Results	No Results Available
Conditions	Tuberculosis|Respiratory Tract Infections|Pneumonia
Interventions	Drug: Azithromycin|Drug: Amoxicillin
Outcome Measures	Diagnostic accuracy of trial-of-antibiotics: Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 against a mycobacteriology reference standard.|Overall clinical benefit of empirical antibiotic treatment in primary care participants with chronic cough: proportion of participants experiencing adverse clinical outcomes|Impact of trial-of-antibiotics on antimicrobial resistance|Diagnostic accuracy of trial-of-antibiotics including participants who did not produce sputum|Economic analysis of use of trial-of-antibiotics
Sponsor/Collaborators	London School of Hygiene and Tropical Medicine|University of Malawi College of Medicine
Gender	All
Age	18 Years and older Â (Adult, Older Adult)
Phases	Phase 3
Enrollment	1875
Funded Bys	Other
Study Type	Interventional
Study Designs	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Diagnostic
Other IDs	15232
Start Date	February 25, 2019
Primary Completion Date	Jun-20
Completion Date	Jun-20
First Posted	June 4, 2018
Results First Posted	
Last Update Posted	August 15, 2019
Locations	University of Malawi College of Medicine, Blantyre, Southern, Malawi
Study Documents	
URL	https://ClinicalTrials.gov/show/NCT03545373

Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis (TB) in primary care adult patients versus risk of antimicrobial resistance (AMR)

Short title:	**A**ccuracy and **C**onsequences of using **T**rial-of-antibiotics for **TB** diagnosis
Acronym:	ACT-TB Study
Trial registration:	
Protocol version:	3.0, 19 Feb 2019
Chief Investigator:	Titus H Divala London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT Tel: +44 740 523 1847 Email: titus.divala@lshtm.ac.uk
Co-Investigators:	Katherine L Fielding, Neil French, Derek J Sloan, Elizabeth L Corbett
Collaborators:	Marriott Nliwasa, Augustine Choko, Ankur Gupta-Wright, Jennifer Cornic, Jon Øyvind Odland, Chisomo Msefula, Hendramoorthy Maheswaran
Sponsor:	London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office: London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT Tel: +44 207 927 2626 Email: RGIO@lshtm.ac.uk
Funding:	Helse Nord RHF Tromsø, Norway; Tel: +47 97065144 Email: Hanne.Husom.Haukland@helse-nord.no
Study Coordination Centre:	University of Malawi College of Medicine Private Bag 360 Chichiri, Blantyre, Malawi Tel: +2651871911 Email: rscdirector@medcol.mw

This trial will adhere to the principles outlined in the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

Table of contents

1 Abbreviations

ACASI	Audio Computer Assisted Self-Interview
AE	Adverse Event
AMR	Antimicrobial Resistance
AR	Adverse Reaction
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CEACs	Cost-Effectiveness Acceptability Curves
COMREC	University of Malawi College of Medicine Research and Ethics Committee
CXR	Chest X-Ray
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety and Monitoring Board
GLM	Generalised Linear Model
HIV	Human Immunodeficiency Virus
HRQoL	Health Quality of Life
LAM	Urine Lipoarabinomannan Assay
LJ	Lowenstein-Jensen
LSHTM	London School of Hygiene & Tropical Medicine
MDA	Mass Drug Administration
MGIT	Mycobacteria Growth Indicator Tube

MTB or M.tb	*Mycobacterium tuberculosis*
NMBs	Net Monetary Benefits
NTM	Non-Tuberculous Mycobacteria
NTP	National Tuberculosis Control Program
NTS	Non-Typhoidal Salmonellae
PCP	Pneumocystis Jiroveci
PLHIV	People Living With HIV
PTB	Pulmonary Tuberculosis
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOC	Standard of Care
STGG	Skim Milk Tryptone Glucose Glycerol
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
WHO	World Health Organization
WTP	Willingness to Pay

2 Study Summary

Title	Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis (TB) in primary care adult patients versus risk of antimicrobial resistance (AMR)
Design	Three arm (625 per arm) individually randomised (1:1:1), open-label controlled clinical trial investigating standard care diagnostic approach for tuberculosis. The trial will not use any unlicensed products.

Objective	**Outcomes**
Primary	
1. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults with prolonged cough at primary care level in Malawi.	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among participants submitting at least one sputum specimen
2. To determine the overall clinical benefit of giving empirical antibiotic treatment in primary care participants with chronic cough.	Proportion of participants experiencing at least one of the following adverse outcomes by Day 29: 1) death 2) hospitalisation 3) missed TB diagnosis 4) HIV care loss to follow up 5) TB care loss to follow up
Secondary	
3. To evaluate using nasopharyngeal Streptococcus pneumonia, the effect of a trial-of-antibiotics on selection for antimicrobial resistance.	Risk of acquiring nasopharyngeal Streptococcus pneumonia isolates resistant to any of the commonly used groups of antimicrobials by Day-29.
4. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults with prolonged cough at primary care level in Malawi.	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among all

	randomised participants, with those who could not provide sputum classified as mycobacteriologically negative.
5. To estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other.	• Incremental cost per quality adjusted life year gained • Total direct medical costs per participant over 56 days • Eq-5D utility score
Exploratory	
Our exploratory analyses will be comparisons between the azithromycin and amoxicillin arms for all our primary and secondary outcomes.	
Population	Adults presenting to primary care centres in Malawi reporting cough.
	Inclusion criteria: • Ambulatory clinic attendees presenting with cough for ≥ 14 days • Aged at least 18 years • Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period. Exclusion criteria: • Self-reported allergy to study medications • Acute danger signs defined in national TB treatment guidelines • Tuberculosis treatment or isoniazid preventive therapy in the last 6 months • Treated with antibiotics, other than co-trimoxazole prophylaxis, for the current illness or within the past 14 days
Treatment	**Arm 1**: Azithromycin 500mg once daily for 3 days commencing on randomization day. **Arm 2**: Amoxicillin 1 g 3 times daily for 5 days commencing on randomization day. **Arm 3**: Standard of care in current national guidelines for patients presenting with cough and without danger signs (No treatment until re-evaluation with sputum TB test results)
Duration	We will give treatments on the randomisation day (Day-1) and perform follow up activities on days 8, and 29.

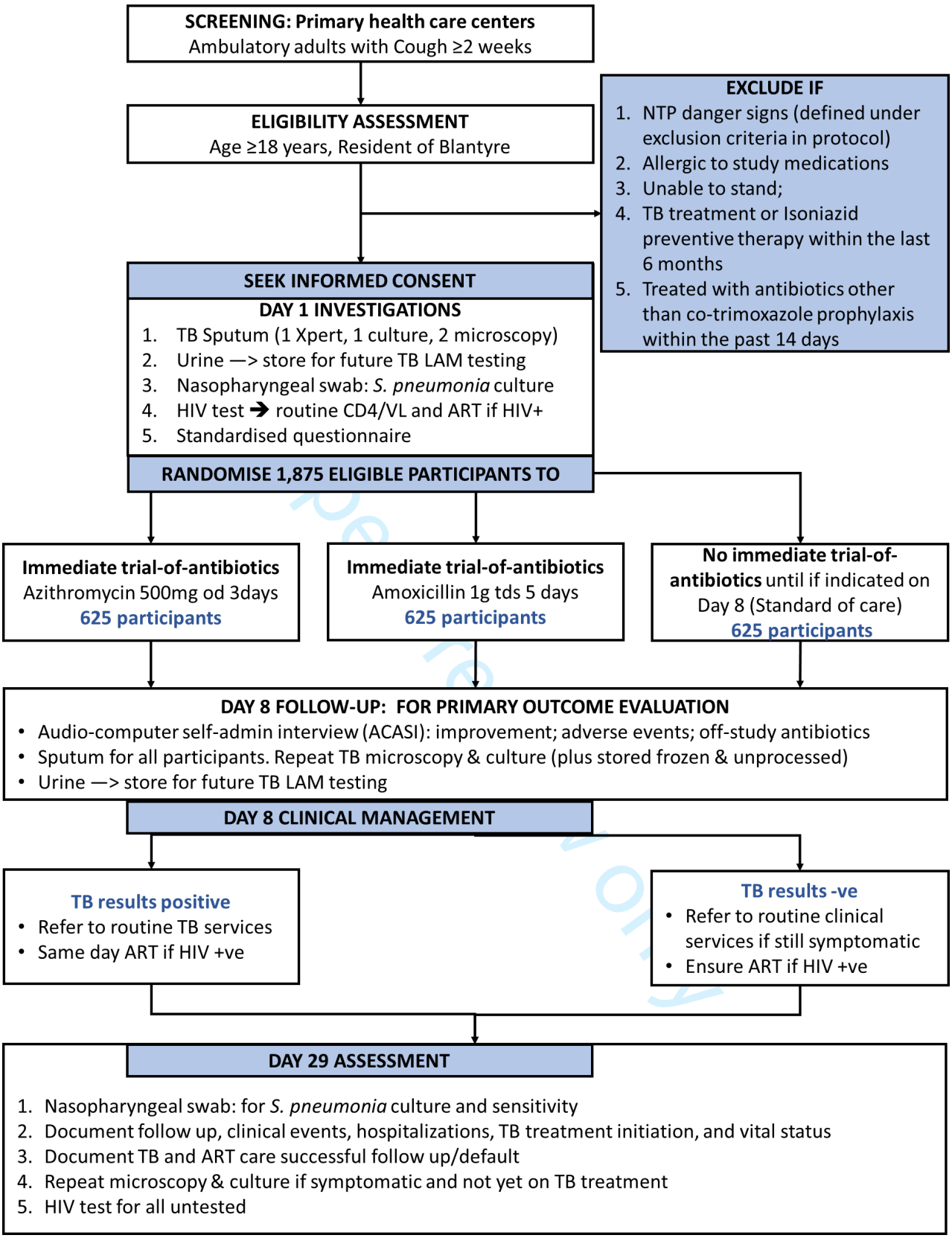


Figure 1: Flow diagram for the planned clinical trial in Blantyre, Malawi

3 Introduction

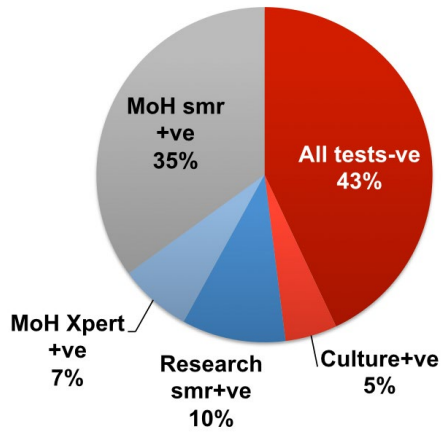
3.1 Background

Antimicrobial resistance is a growing crisis, becoming in 2016 one of only four health topics ever to be discussed at the United Nations General Assembly.[1-4] Tuberculosis is the leading global infectious cause of death in adults,[5] with approximately 10.4 million cases and 1.8 million deaths in 2015.[6] The high case-fatality rate in part reflects suboptimal diagnostics(Figure 2).[7-10]

Diagnosis method	Percentage
Mycobacteriology	57%
Clinical	43%

A. WHO annual TB notifications (WHO 2017 TB Report)

B.



Nliwasa et.al

Figure 2: method of diagnosis for TB notifications globally (A) and in Blantyre, Malawi (B)

To complement the suboptimal diagnostics, standard diagnostic algorithms in resource-limited settings include a “trial-of-antibiotics” (Figure 3). This is a course of broad-spectrum antibiotics, with negligible *Mycobacterium tuberculosis* activity, given to patients with symptoms such as cough in order to “rule-out” or “rule in” tuberculosis.[11-13] Patients with negative sputum mycobacteriology and responded to antibiotic treatment are considered tuberculosis negative while those who remain symptomatic are deemed likely to have tuberculosis and undergo further evaluations leading on to receiving tuberculosis treatment.

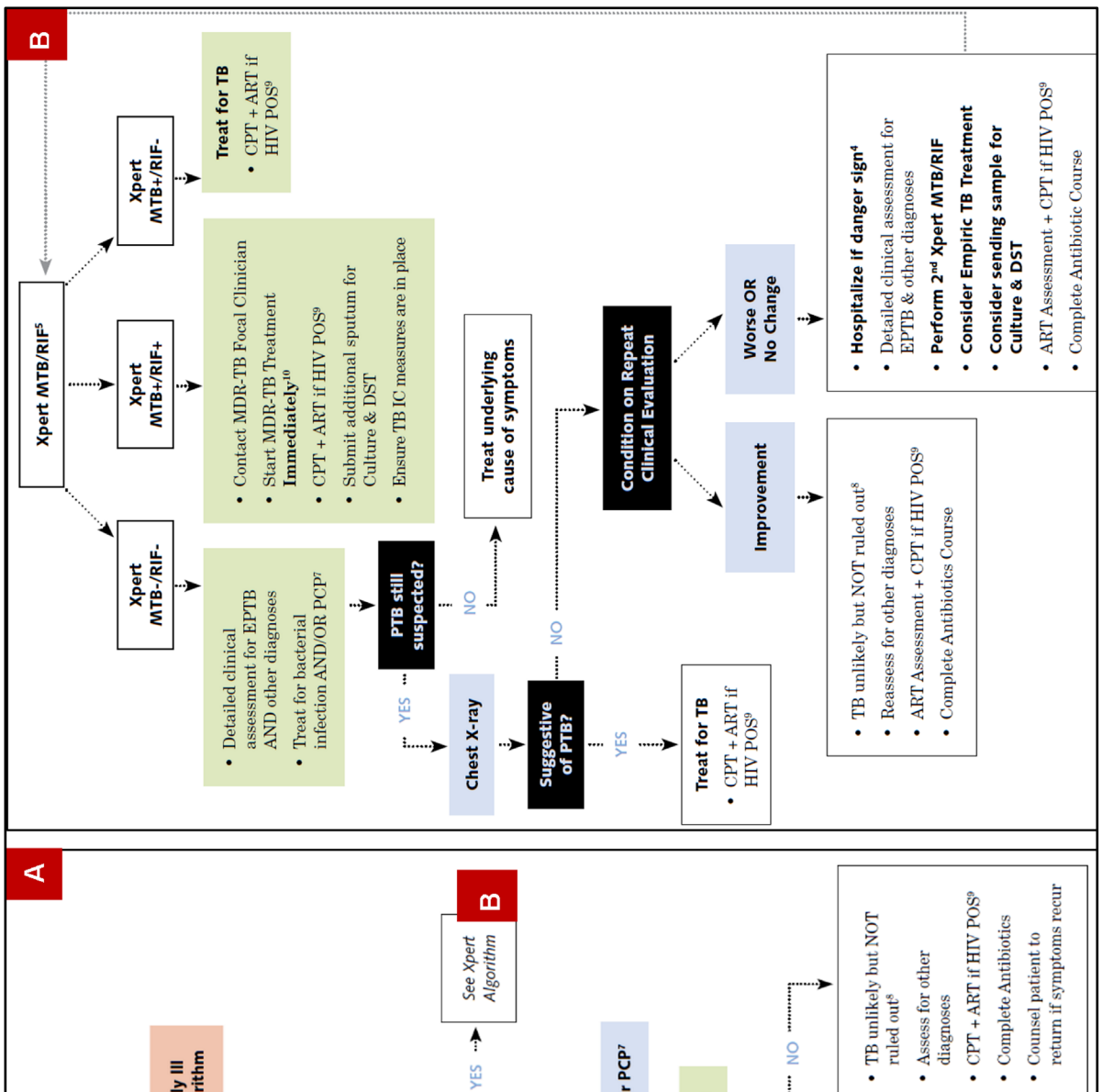


Figure 3: Implementation of trial-of-antibiotics (marked with red boxes) in Malawi TB diagnostic algorithm, National TB control program (NTP)

Approximately 26.5 million course of antibiotics are prescribed in the diagnosis of the 5.3 million smear negative tuberculosis registrations per annum (Figure 4).[6] This estimate is based on an average of 5 antibiotic courses per sputum-negative treatment initiation, with 2 courses given to the patients before tuberculosis treatment,[8] and the other 3 courses accounting for patients whose symptoms resolved and tuberculosis was ruled out.[14].

Wilkinson et al[14] prescribed 120 + 74 courses of trial-of-antibiotics to diagnose 40 smear-negative TB patients (a typical ratio of ~1:5).[8] If generalizable, then for 5.3 million annual smear-negative TB registrations globally ~5 x 5.3 million trial-of-antibiotics courses (26.5 million) will have been prescribed.

Enrolled	**280**	
TB smear microscopy positive		160
Given trial-of-antibiotics (amoxicillin)	**120**	
Improved, declared TB negative		46
Given trial-of-antibiotics (erythromycin)	**74**	
Improved, declared TB negative		34
Treated for smear negative TB	**40**	

Wilkinson et.al Int J Tuberc Lung Dis. 2000

Figure 4: Quantifying number of trial-of-antibiotics courses prescribed per year using data from Wilkinson et.al and WHO TB Report 2016

Despite this widespread use, there is no randomised controlled trial evidence supporting the diagnostic accuracy of trial-of-antibiotics. There is also a dearth of evidence on their impact on antimicrobial resistance or patient clinical outcomes.

3.2 Systematic literature review

We performed a systematic literature review to determine the sensitivity and specificity of using a trial-of-antibiotics compared to sputum mycobacteriology for diagnosis of PTB. We also wanted to describe how trial-of-antibiotics tits into TB diagnostic algorithms: timing of prescription; type, duration, and number of antibiotic prescriptions; and how response to treatment is measured. We searched MEDLINE, Embase, and Global Health using the Ovid platform to identify studies meeting the following criteria:

Population	Adult patients with symptoms suggestive of pulmonary tuberculosis
Intervention	Routinely prescribed broad-spectrum oral antibiotics without MTB activity, and given as part of evaluation of pulmonary TB
Outcome	sensitivity and specificity of the intervention in comparison with any mycobacteriology test
Study design	Any design with prospective component allows evaluation of the outcome of the intervention
Time frame	Studies published after WHO declaration of TB as a 'global emergency' (1993)
Language	English, lack of translation capacity

We identified 7,064 articles from a systematic search on MEDLINE, Embase, and Global Health using the Ovid platform. Of these studies, 12 were eligible for narrative synthesis and seven had suitable data for meta-analysis. None of the studies was an RCT and all the observational studies were small and not primarily designed to address the benefits and consequences of trial-of-antibiotics. Unlike our proposed RCT, most of the published work was from hospital setting or in specialised clinics. Most studies used amoxicillin and some studies prescribed a subsequent course of antimicrobials either before or after assessing for improvement. The definition of improvement from baseline clinical state was largely subjective: it was based on self-report, clinical examination, radiological assessment or a combination.

There is no consensus on the sensitivity and specificity of trial-of-antibiotics across studies with estimates ranging from 43% to 91% for sensitivity and 41% to 82% for specificity (shown below).

Population, Study		Sensitivity, 95% CI			Specificity, 95% CI		
237	Wilkinson et al 1997	0.5	0.37	0.64	0.82	0.76	0.87
120	Wilkinson et al 2000	0.83	0.71	0.91	0.56	0.44	0.67
204	Kudjawu et al 2006	0.91	0.83	0.96	0.65	0.56	0.73
1000	Kamran et al 2006	0.72	0.62	0.8	0.41	0.38	0.44
264	Soto et al 2011	0.43	0.32	0.55	0.68	0.63	0.72
439	Soto et al 2013	0.46	0.34	0.58	0.6	0.53	0.66
440	Padmapriyadarsini et al 2	0.7	0.55	0.8	0.69	0.64	0.73

We could not identify any RCT, the current literature only has small studies, with trial-of-antibiotics not being the primary focus of investigation in most cases. There is limited data for primary care settings as most of the work was in hospital setting. None of the studies addressed AMR. Therefore, despite widespread use, the approach, the value and consequences of having trial-of-antibiotics in TB diagnostic algorithms, remains to be established.

3.3 Planned study

To address the evidence gaps related to a) accuracy, b) antimicrobial resistance, and c) impact on clinical outcomes), we propose to conduct a randomised controlled clinical trial recruiting adult patients presenting to primary care centres in Blantyre, Malawi with history of cough for at least 2 weeks. After excluding those with danger signs we will randomise participants to receiving or not receiving trial-of-antibiotics (azithromycin or amoxicillin) from Day-1 to determine diagnostic accuracy (specificity) against mycobacteriology reference standard (smear microscopy, Xpert/MTB/RIF and culture).

For secondary outcomes, we will also compare between arms differences in antimicrobial resistance and clinical outcomes (risk of death, hospitalisation, TB misdiagnosis, and loss to HIV or TB care follow up) at Day-29. To our knowledge this will be the first randomised controlled trial to address these questions in over 20 years of systematic use of trial-of-antibiotics without strong evidence base.

3.4 Rationale for current study

3.4.1 Accuracy of trial-of-antibiotics

As an approach that is being used on such a large scale, trial-of-antibiotics should ideally have a strong evidence-base (supported by reference mycobacteriology) of how much diagnostic and/or clinical improvement it brings to the TB diagnostic algorithm.[15,16] This will be among the most important considerations when deciding whether it is worth the trade-off with potential for AMR. Such evidence could come from an RCT or a well-designed prospective study.[15-17] However, despite being in use for more than 20 years, we have not identified any such clinical trial, and even the observational evidence is highly limited and of insufficient quality and quantity to definitively address the question.

There is also no guidance on antibiotic choice beyond a recommendation to avoid those with anti-tuberculosis activity (like fluoroquinolones). Another key area that lacks clarity is lack of a clear definition for clinical resolution when determining the outcome of trial-of-antibiotics. Clinical resolution is the basis for decisions that follow (i.e. discontinue follow up or proceed Antimicrobial resistance and trial-of-antibiotics

Antimicrobial resistance can be either intrinsic or acquired. The risk of acquired resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been previously investigated, although previous work has shown that empirical antibiotics can drive rapid emergence of AMR.[18,19] For example, co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010.[20] Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniae*, but with increased macrolide-resistance 6 months later.[21,22]

In our study, the AMR risks of empirical antibiotic prescriptions (azithromycin and amoxicillin arms of the RCT) are justified because of the widespread use of this approach for amoxicillin, and the low potential clinical impact and short-lived effects of use of azithromycin on AMR, given the limited use of macrolides in Malawi. Mathematical modelling work suggests that macrolide resistance can successfully be eliminated by intra-species competition alone (fitness cost) within 5 years of last use.[23]

3.4.2 Antimicrobial resistance and trial-of-antibiotics

Antimicrobial resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been investigated before. Previous work has shown that empirical antibiotics can drive rapid emergence of antimicrobial resistance.[18,19] Co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010[20] also shown in Table 1. Mass drug administration of azithromycin for trachoma control initially

reduces nasopharyngeal carriage of *Streptococcus pneumoniae*, but with increased macrolide-resistance 6 months later.[21,22]

We will investigate antimicrobial resistance in nasopharyngeal *S. pneumonia* by randomisation arm and cumulative antibiotic exposure to assess the extent to which brief exposure drives antimicrobial resistance during diagnostic work-up for tuberculosis. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient window for investigating antimicrobial resistance.[24] *S. pneumonia* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract and has well documented laboratory investigation procedures in place.[25] As exploratory analyses, we will also assess nasopharygeal colonization and antimicrobial resistance in relation to tuberculosis treatment and HIV status.

Table 1 Resistance patterns of common aetiologies of pneumonia to commonly used antimicrobials in Blantyre, Malawi

		Gram positive		Gram negative			
Organism		Streptococcus pneumoniae	Staphylococcus aureus	Haemophilus influenzae	Klebsiella pneumoniae	Escherichia coli	Pseudomonas aeruginosa
Prevalence		15.6%	6.6%	0.9%	4.4%	0.1%	1.5%
Resistance percentage	amoxicillin	*	*	58%	100%	94%	100%
	penicillin	21%	*	*	*	*	*
	co-trimoxazole	98%	40%	100%	92%	94%	75%
	chloramphenicol	21%	2%	92%	48%	61%	100%
	Erythromycin	2%	30%	*	*	*	*
	tetracycline	38%	35%	*	*	*	*
	Ceftriaxone	*	*	0%	90%	30%	100%
	Ciprofloxacin	*	*	NA	705	31%	24%

*not routinely tested

2016 data from hospitalised febrile patients at Queen Elizabeth central hospital (Blantyre, Malawi) as reported by the MLW Clinical research laboratory (unpublished).

3.4.3 Potential benefits of antibiotics

In areas with high HIV prevalence, empirical antibiotics during tuberculosis investigations could be life-saving: mortality immediately before and after tuberculosis diagnosis is high, [7,26] and is often secondary to severe bacterial infections.[26-28] The leading aetiologies of infection and death on tuberculosis treatment as well as among outpatients with tuberculosis-like symptoms are *Streptococcus pneumoniae* and non-typhoidal salmonellae (NTS): both can present with cough (primary cause) or as co-morbidities (super-infections) in patients presenting with active *Mycobacterium tuberculosis* (*M.tb*) disease.[26-28] If effective treatment of this type of life-threatening primary/super-infections reduces mortality during the diagnostic work-up of suspected TB in people living with HIV (PLHIV), then empirical use of broad-spectrum antibiotics would be indicated for this purpose alone, irrespective of any diagnostic contribution to TB treatment decisions. In this context,

azithromycin may be the most effective arm, as Salmonella infections are highly sensitive to azithromycin, but not to amoxicillin.[29]

3.4.3.1 Measures of clinical benefit of trial-of-antibiotics

In this study, we will investigate the overall clinical benefit of trial-of-antibiotics by comparing the risk of any of death, hospitalisation, missed TB diagnosis, and loss to HIV or TB care follow up by Day 29. Although all these events are potential consequences of trial-of-antibiotics, grouping them as a single composite endpoint may only appropriately represent the effect of the intervention 1) there are similarities in the importance patients would attach to each of its components and 2) the components occur with similar frequencies in the patient population.[30]

The impact of antibiotics on hospitalisation and mortality causing illnesses is as described above. Both these outcomes are important with their similarity hinged on the fact that hospitalisation event predicts mortality. In patients with chronic cough, frequencies of mortality and that of hospitalization over a two months period are similar, ranging from 2 to 6%.[31]

TB misdiagnosis becomes a concern because of the potential for misclassification in either direction –false positive or false negative. False positive diagnosis in the context of trial-of-antibiotics would occur when the underlying pathology for the respiratory symptoms is not responding to the antibiotic, which can be secondary to either AMR or the illness not being of bacterial origin. On the other hand, patients would be prone to a false negative result had both TB and a susceptible bacterial infection. If the symptoms were largely driven by the susceptible bacterial infection, their symptoms will improve and would be declared TB negative. TB is a life-threatening illness, missing its diagnosis can therefore lead to death which is more important to an individual patient than taking TB chemotherapy with a false positive TB diagnosis. We will therefore include only missed TB diagnoses in the composite clinical outcome. Unpublished data from Blantyre shows that the frequency of missed TB diagnosis under routine care settings is approximately 5% which is similar to that of death and hospitalisation.

Experiencing respiratory symptoms prompts care seeking which often leads to TB and HIV diagnosis and respective long-term treatment and follow up going way beyond resolution of initial symptoms. We hypothesize that giving antibiotics and curing the respiratory illness that prompted them to seek diagnosis, reduces care-seeking motivation. Care seeking is often driven by having symptoms and perceivable benefits of care often fade away as symptoms shed off. We will estimate the frequency of HIV and TB care loss to follow up at 1 month during the pilot study. The pilot study will also assess the combined risk of all the five components of the clinical benefit outcome.

3.4.4 Important subgroups

Response to trial-of-antibiotic- in patients with bacteriologically confirmed tuberculosis (i.e. false-negatives/low sensitivity from the perspective of TB diagnosis) may relate to multiple super-infections and so this phenomenon may vary by HIV status, since multiple concurrent infections are a hallmark of advanced HIV immunosuppression, and commonly identified in patients with suspected TB in the pre-ART era.[8,27] More recently, in Malawi, 45% of adults who presented to primary care with prolonged cough (≥2 weeks) were HIV-positive, of whom only ~20% started TB treatment on the basis of positive mycobacteriology.[31] As such, the benefits and consequences of trial-of-antibiotics may vary by HIV status and by subsequent TB treatment decisions. We will, therefore, include a pre-specified sub-analysis of trial outcomes stratified by HIV and ART status.

3.5 Choice of study interventions

Our trial will compare azithromycin and amoxicillin to standard of care. We propose 2 different antibiotic arms for the following reasons: -

a) Macrolides, including azithromycin, are rarely used in Malawi because of their higher manufacturing costs. However, they do provide a more effective treatment of community-acquired pneumonia than the standard antibiotic by Ministry of Health for trial-of-antibiotic (amoxicillin), because of low levels of acquired macrolide-resistance in bacterial isolates in Malawi,[29] reflecting low rates of past exposure to this class of drugs, and also better intrinsic coverage of "bacterial cause of pneumonia including "atypical" intracellular organisms such as *mycoplasma* species.

Although viral pneumonias, *Pneumocystis jiroveci* (PCP) and non-infectious causes of cough will still not be expected to respond to azithromycin, this arm should then provide the highest possible diagnostic discrimination for bacterial vs mycobacterial causes of cough. The starting point of low pre-existing (acquired) resistance will also facilitate investigation of AMR acquired during trial-of-antibiotics. However, the trial will have limited national relevance in Malawi without comparison to an antibiotic in programmatic use.

b) Amoxicillin is low cost option that is still a recommended treatment for community-acquired pneumonia in most settings, including UK, despite potential treatment failure from bacterial pneumonia due to organisms with intrinsic ("atypicals") or acquired (common in gram-negative organisms, and *Staphylococcus aureus*) penicillin resistance.[29] This arm reflects the true standard of care (SOC) currently in widespread use in Malawi and many other low-income countries, and so provides data of immediate programmatic relevance and also a starting point to investigate exacerbation of pre-existing AMR pressure. If there is a marked difference between

the azithromycin and amoxicillin arms, then there will also be important health economic considerations of relevance to many national TB programmes beyond Malawi.

Azithromycin provides effective treatment for community-acquired pneumonia[32-34] and has negligible activity against *M.tb.*[35,36] As discussed above, macrolides are not commonly used in Malawi. Azithromycin has an excellent safety profile and is used for mass drug administration (MDA) in communities prone to trachoma. Azithromycin used for MDA in Ethiopia reduced inter-current infections[21,37] and death in children,[38,39] supporting the safety of using this drug for our trial.[7]

Amoxicillin is the first line treatment for outpatient management of pneumonia in Malawi and is commonly used for trial-of-antibiotics. We anticipate higher specificity for azithromycin than amoxicillin, due to broader coverage of "atypical pneumonia" organisms, and salmonella species, but with the 2 antibiotics arms having "equipoise" due to lack of previous head-to-head comparison.[27]

3.6 Nasopharyngeal pneumococcus for AMR

Streptococcus pneumonia is a major cause of morbidity and mortality in children and adults.[20,29,40,41] Asymptomatic nasopharyngeal carriage of *S. pneumoniae* is common and a prerequisite for the occurrence and transmission of invasive pneumococcal disease.[42,43] Since carriage is more common than the invasive *S. pneumoniae* disease it forms a basis for establishing circulating serotypes, resistance patterns, and evaluation of vaccine effectiveness.

The other key advantage is the existence of globally accepted laboratory procedures for assessing and interpreting pneumococcal resistance. Our laboratory (in Malawi-Liverpool Wellcome Trust) has carried out pneumococcal work for decades with outstanding quality assurance reputation.

3.7 Objectives and outcomes

In Table 2 below, we present study objectives together with corresponding outcomes. We have clarified the outcomes with detailed definitions and planned analyses under "statistical approach" section.

Table 2: study objectives and outcomes

Objective	**Outcome**
Primary	
1. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-

with prolonged cough at primary care level in Malawi.	antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among participants submitting at least one sputum specimen
2. To determine the overall clinical benefit of giving empirical antibiotic treatment in primary care participants with chronic cough.	Proportion of participants experiencing at least one of the following adverse outcomes by Day 29: 1) death 2) hospitalisation 3) missed TB diagnosis 4) HIV care loss to follow up 5) TB care loss to follow up
Secondary	
3. To evaluate using nasopharyngeal Streptococcus pneumonia, the effect of a trial-of-antibiotics on selection for antimicrobial resistance.	Risk of acquiring nasopharyngeal Streptococcus pneumonia isolates resistant to any of the commonly used groups of antimicrobials by Day-29.
4. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults with prolonged cough at primary care level in Malawi.	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among all randomised participants, with those who could not provide sputum classified as mycobacteriologically negative.
5. To estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other.	• Incremental cost per quality adjusted life year gained • Total direct medical costs per participant over 56 days • Eq-5D utility score
Exploratory	
Our exploratory analyses will be comparisons between the azithromycin and amoxicillin arms for all our primary and secondary outcomes.	

4 Study design, participants, and statistical approach

4.1 Study design

This is a three arm (625 per arm) individually randomised (1:1:1), open-label controlled clinical trial investigating accuracy and broader clinical, and antimicrobial resistance impact of using trial-of-antibiotics to "rule out" tuberculosis among adults presenting with cough at primary care centres in Malawi.

4.2 Study setting

We will screen adults aged at least 18 presenting to primary care centres in Blantyre, Malawi. Blantyre has an estimated adult HIV prevalence of 12.7% (95% CI: 11.9 to 13.6) and an estimated tuberculosis prevalence of 1,014 per 100,000 (95% CI: 486 to 1,542).[44]

4.3 Standard of care

The standard of care in national guidelines from the NTP for primary care patients presenting with cough and are otherwise well (no danger signs) is to take sputum x 2 for smear microscopy or Xpert and ask them to return for results, typically 3 days - 1 week later (Figure 3 and 5). The Malawi tuberculosis diagnostic algorithm recommends use of broad-spectrum antibiotics as trial-of-antibiotics after negative sputum tests are provided to the patient, if they remain symptomatic.

However, more commonly this algorithm is adapted in the outpatient setting to combine prescription of antibiotics (usually amoxicillin) with sputum collection at the first visit, to save the patient from making separate visits: thus, our amoxicillin arm is the most common standard-of-care in Malawi, while the no-antibiotic arm is the NTP recommended standard-of-care.

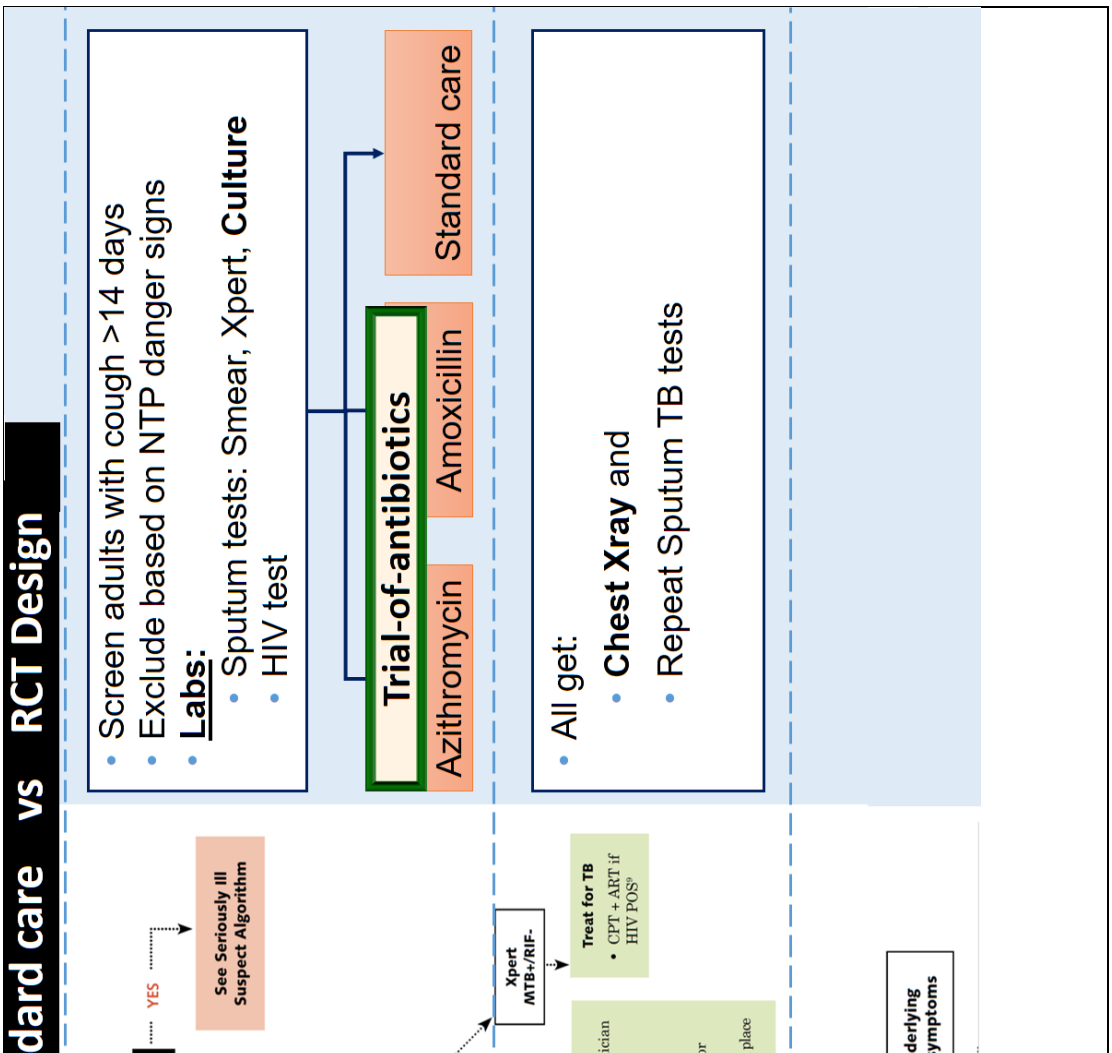


Figure 5: A comparison of standard of care (Malawi NTP guidelines) and the RCT design with respect to timing of trial-of-antibiotics and study procedures

4.4 Eligibility criteria

We will offer enrolment to patients who satisfy the following inclusion and exclusion criteria.

4.4.1 Inclusion Criteria

- Ambulatory clinic attendees presenting with cough for at least 14 days
- No previous formal consultation for current illness (initial presentation)
- Aged at least 18 years
- Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period.

4.4.2 Exclusion Criteria

- Self-reported allergy to study medications
- Danger signs (WHO/Malawi NTP): respiratory rate > 30/min, temperature >39^{o}C, Heart rate >120/minute, confused/agitated, respiratory distress, systolic blood pressure <90 mmHg, inability to walk unassisted
- Treated with antibiotics other than co-trimoxazole prophylaxis within the past 14 days
- TB treatment or Isoniazid preventive therapy within the last 6 months

4.5 Interventions

We will have two active study arms receiving trial-of-antibiotics at enrolment (azithromycin and amoxicillin) and a standard of care arm of no trial-of-antibiotics. In this study, the goal is to investigate the role of these antibiotics as they are used in TB diagnostic algorithms, as "trial-of-antibiotics," to exclude TB in symptomatic patients. The study is likely to be underpowered to detect differences between the 2 antibiotic arms will only be compared for exploratory outcomes.

4.5.1 Name and description of intervention arms

The study will have three arms as follows:

- Arm 1: Immediate trial-of-antibiotics with Azithromycin 500mg once daily for 3 days.
- Arm 2: Immediate trial-of-antibiotics with Amoxicillin 500 mg 3 times daily for 5 days.
- Arm 3: Standard of care

4.5.2 Legal status of drugs used in intervention arms

Both azithromycin and amoxicillin are registered for use in Malawi and United Kingdom, with both Arms 1 and 2 regimens being UK-recommended community-acquired pneumonia treatment.

4.5.3 Summary of Product Characteristics

Appendix 3 includes current versions of package insets for azithromycin and amoxicillin. We will review and update (when applicable) the package inserts annually with each ethics continuing review.

4.5.4 Drug Storage and Supply

We will procure study products from Durbin PLC (DURBIN PLC 180 Northolt Road South Harrow Middlesex HA2 0LT). Azithromycin will be manufactured by Sandoz limited or other pharmaceutical companies recognised in United Kingdom where Durbin is based. Amoxicillin will be manufactured by Medopharm private limited or other pharmaceutical companies recognised in United Kingdom where Durbin is based. Both azithromycin and amoxicillin are stable at room temperature. We will therefore ship and store in ambient conditions.

4.5.5 Preparation and labelling of study drugs

Study products will be stored at Malawi Liverpool Wellcome Trust Pharmacy. The pharmacy team will be responsible for packing and labelling.

4.5.6 Known drug reactions (adverse events)

Azithromycin and amoxicillin are already widely used in Malawi and are well tolerated. Rare side effects for azithromycin include nervousness, dermatologic reactions including Stevens–Johnson syndrome, anaphylaxis and prolonged QT interval. Rare side-effects for amoxicillin are mental state changes, light-headedness, photosensitivity and severe allergic reactions.

4.5.7 Concomitant medication and interaction with other therapies

We do not have any restrictions with respect to concomitant medications apart from those listed in the exclusion criteria. We expect some participants to be on HIV antiretroviral drugs and some may subsequently start tuberculosis therapy. Important interactions therefore would be those with HIV antiretroviral drugs and tuberculosis therapy. There is no moderate or major interaction between either azithromycin or amoxicillin with the classes of HIV antiretroviral drugs, tuberculosis therapy, and antimalarial drugs used in Malawi.

4.5.8 Trial restrictions

We do not require participants to have any dietary restrictions. We will also accept co-administration with contraception. Our trial interventions can safely be used in pregnancy, so we will include pregnant women should they be eligible.

4.5.9 Assessment of compliance

On Day-8, we will document self-reported compliance adherence of study products.

4.5.10 Withdraw of interventions

The investigator may also terminate a participant from study product if indicated by an adverse reaction. If a participant stops taking study product either voluntarily or by investigator decision, they will be encouraged to remain in follow up and their data will form part of intention to treat analyses.

4.6 Statistical approach

We will summarise the processes of recruitment including non-eligibility and reasons of exclusion in a CONSORT flow chart. We will describe the study participants by their baseline characteristics which we will report for each arm. We will perform analyses of all our outcomes based on an intention to treat analysis (using the arm patient was randomised to), adjusting for centre. We will make the following comparisons:

i) azithromycin or amoxicillin versus standard of care

ii) azithromycin versus standard of care

iii) amoxicillin versus standard of care

We will perform data cleaning and analysis using Stata release 15 (Stata Corp, College station, Texas, USA).

The following are descriptions of each outcome and corresponding statistical approach. The statistical approach will be expanded in a detailed statistical analysis plan, separate to the protocol, which will be finalised before unblinding the study data.

4.6.1 Primary outcome

4.6.1.1 Primary outcome 1: Specificity of trial-of-antibiotics versus mycobacteriology

Outcome definition

Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 ACASI against a mycobacteriology reference standard (b+d in Figure 6).

To minimise ascertainment bias in ascertaining this endpoint, the evaluation of improvement of baseline symptoms will be captured using a self-interview platform: Audio Computer Assisted Self-Interview (ACASI). After orientation, the participant will be left alone in the room to interact with the computer. ACASI on Day-8 will precede all other interaction with research staff and clinical assessment/decision making.

Mycobacteriology reference standard will be defined in participants with at least one specimen with a valid result on days 1 and 8 as:

- **TUBERCULOSIS-POSITIVE**: if at least one positive smear microscopy, Xpert/MTB/RIF, or MTB culture on sputum samples taken.
- **TUBERCULOSIS-NEGATIVE**: none of the day 1 and day 8 sputum samples are positive on smear microscopy, GeneXpert MTB/RIF, or MTB culture.

To minimise bias, the mycobacteriology will be performed by a high-quality research laboratory in the University of Malawi College of Medicine by staff with no access to participant treatment allocation information or ACASI results.

ACASI Response interpretation

The responses of participants during the ACASI interview will be classified as:

- **TUBERCULOSIS-POSITIVE:** participant reports lack of improvement of symptoms they had on Day 1.
- **TUBERCULOSIS-NEGATIVE:** participant reports improvement of symptoms they had on Day 1.

Reference Result: any tuberculosis positive sputum result from Day-1 and Day-8 visit samples defines pulmonary tuberculosis positive (*smear microscopy, Gene Xpert, or MTB Culture*)

ACASI Response
Lack of improvement of from the symptoms they had at baseline documented on Day-8 using ACASI* defines tuberculosis positive

	+ve	-ve
+ve (Did not improve)	a	b
-ve (Improved)	c	**d**

Primary outcome: a comparison of **d / (b+d)** proportions in treatment versus standard of care as follows:

i) azithromycin or amoxicillin versus standard of care
ii) azithromycin versus standard of care and
iii) amoxicillin versus standard of care

* Audio Computer Assisted Self-Interview (ACASI) validated during a pilot study.

Figure 6: Ascertainment of diagnostic value of trial-of-antibiotics

Estimation of measures of effect

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for center. For each comparison, we will report 95% Confidence Intervals and Chi-square p-values. In pre-specified

subgroup analysis, we will estimate the treatment effects stratifying by baseline HIV status. If the GLM model does not converge, we will use logistic regression to estimate the treatment effect using an odds ratio.

Participants without mycobacteriology

Primary analyses will be limited to participants who have at least one valid sputum sample result from all samples collected on visits Day-1 and Day-8. However, in real-life, ~15% fail to produce sputum, we will as a secondary outcome, perform all the analyses described for primary outcome with these participants defined as mycobacteriology negative. Further sensitivity analyses with urine lipoarabamannan antigen (LAM) results will include them in mycobacteriology definition.

4.6.1.2 Primary outcome 2: Clinical benefit of trial-of-antibiotics

Outcome definition

Proportion of participants experiencing at least one of the following adverse outcomes: death, hospitalisation, TB misdiagnosis, HIV care loss to follow up, TB care loss to follow up. The definitions of the components of this composite clinical outcome are defined in the table below:

Outcome component	Definition
death	Proportion of deaths by Day 29
hospitalisation	Proportion hospitalised for any cause by Day 29
missed TB diagnosis	Day 29 proportion of participants meeting standard **mycobacteriological and radiological** TB definitions but incorrectly classified as TB negative and not yet on TB treatment by Day 29.
HIV care loss to follow up	Proportion of newly identified (Day 1) HIV positive participants not continuing with care by Day 29
TB care loss to follow up	Proportion of newly identified (Day 1/Day 8) TB positive participants who were put on treatment but were not continuing with treatment and follow up by Day 29

Estimation of measures of effect

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for primary care center. For each comparison, we will report 95% Confidence Intervals and Chi-square p-values. If the

outcome is rare or if GLM does not converge, we will use logistic regression to model odds and report odds ratios for the following comparisons and their associated report 95% CIs and p-values.

4.6.2 Secondary outcomes

Outcome definitions

1) Risk of acquiring nasopharyngeal Streptococcus pneumonia isolates resistant to any of the commonly used groups of antimicrobials by Day-29. We will exclude those with resistant isolates on both Day-1 and Day-29 from the numerator, as they may not truly represent incident resistance. In the denominator, we will include all randomised participants and perform analysis as intention to treat.
2) Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among all randomised participants, with those who could not provide sputum classified as mycobacteriologically negative.

Estimation of measures of effect

Our secondary outcomes are anticipated to be rare, we will therefore use logistic regression to model odds and report odds ratios for the following comparisons and their associated report 95% CIs and p-values.

4.6.3 Exploratory outcome

Our exploratory analyses will be comparisons between the **azithromycin** and **amoxicillin** arms for all our primary and secondary outcomes.

4.6.4 Planned subgroup analyses

We will perform subgroup analysis for the primary outcome. The important subgroups based on rationale detailed under section 2.4.4, include HIV status, ART status, and PTB treatment. HIV and ART status will be as documented on Day-1 while PTB treatment will be either as:

- TB treatment commenced based on positive baseline (Day-1 and Day-8) mycobacteriology, *or*
- TB treatment commenced within 29 days of enrolment in patients with negative Day1 and Day-8 bacteriology.

The 29 days cut off for clinical decision to treat is to ensure that we only capture TB disease that was present at baseline. 29 days is a reasonable because: TB is a slowly progressing disease

which if positive at Day-29, must have been incident on Day-1; and in routine care setting it can take over a month from presentation to diagnosis of TB.[8]

4.7 Sample size and power

4.7.1 Primary outcome 1: specificity of trial-of-antibiotics versus mycobacteriology

We assume that trial-of-antibiotics (in azithromycin arm or in amoxicillin arm) will correctly classify 60% of mycobacteriology negative participants.[14] We have determined that 400 mycobacteriologically negative (true negatives) participants per arm will provide 80% power to detect a 10% difference in proportion of participants correctly classified as negative by amoxicillin arm or by azithromycin arm (60%) versus standard of care arm (50%). See table 3. We assume that 80% of participants randomised will have negative mycobacteriology,[31] requiring 500 participants to yield the 400 per arm. Assuming that 15% will not be able to produce sputum, and that 5% will not return for Day-8 visit, the sample size is increased to 625 per arm or 1,875 for the whole study.

Table 3: Power and sample size estimation for primary outcome 1

True negatives (mycobacteriology tests negative participants) **b+d**	[1]**p (negatives correctly classified) d/(b+d)**	[2]**effect size**	**power (X^2 difference between independent proportions)**
320	0.60	0.10	69%
400	**0.60**	**0.10**	**80%**
480	0.60	0.10	86%

[1] specificity with either azithromycin or amoxicillin trial-of-antibiotics arms

[2]risk difference (azithromycin arm- standard of care arm)

4.7.2 Primary outcome 2: Incidence of adverse clinical outcome at Day-29

We will use a pilot study to determine the standard of care risk of at least one of death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up. The pilot study is described in section 5.0.

For now, we will assume that there is a 10% risk of experiencing this composite adverse outcome in the standard of care arm, and that loss to follow up by Day-29 will be 10%. With the sample size of 625 participants per arm (based on the primary outcome 1 sample size calculation), and alpha of 0.05, we will be able to detect the difference between intervention and standard of care with 80% power, if the risk in intervention arm is 6% or lower (Table 4).

Table 4: Sample size estimation for clinical benefit outcome

Participants per arm based on primary	**625**
10% loss to follow up by Day-29	562
Outcome risk in standard of care arm	0.10
Desired power	0.80
Alpha	0.05
Required intervention arm risk	**0.06**

4.7.3 Secondary outcomes

1) Incidence of resistant *S. pneumonia* on Day-29

We assume 10% loss to follow up by Day-29, and the rate of *S. pneumonia* isolation from nasopharyngeal swabs in this population is expected to be ~45% at Day-29. The sample size based on the primary outcome (625 per arm) will provides ~253 *S. pneumonia* isolates/arm. In the standard of care arm, with 10% risk of resistant isolates, this translates into 25 cases. For the intention to treat population (the randomised 625 participants/arm) in the standard of care arm the 21 cases of resistant isolates translate into 4% (25/625) risk. With 4% risk in the standard of care group, alpha of 0.05, and using Pearson's Chi-squared test we will be able to detect the impact of the intervention with 85% power if it leads to an increase of risk of resistant isolates from 4% to 8% (or RR of 2, risk difference of 4%) (Table 5).

Table 5: Sample size estimation for AMR outcome

Participants per arm based on primary	**625**
10% loss to follow up by Day-29	563
45% isolation rate for *S. pneumonia*	253
Resistance: 10% of all isolates	25
Overall proportion in standard of care (25/625)	0.04
Effect size (RR =2, or RD=4%)	0.04 to 0.08
Power	**0.85**

4.7.4 Exploratory outcomes

We anticipate that our sample size will be enough for hypothesis generation around our exploratory objectives but may not be enough to provide discriminatory power for comparison of outcomes between arms.

5 Pilot study

This area of research has limited evidence to guide the precise determination of sample size and the practical aspects of the clinical trial making a pilot study an invaluable tool. We have identified the following as key knowledge gaps which require exploration using a pilot study:

1) Among the adult patients presenting to primary care centres with cough for at least 2 weeks what proportion gets antibiotics:

- **a.** before clinic presentation?
- **b.** on first clinic visit?
- **c.** on follow up clinic visit after mycobacteriology results?

2) Following antibiotic treatment, how do patients report their clinical response? What are the best questions to ask patients post-antibiotic treatment to determine if they have improved or not? How best can we deliver these questions via Audio Computer Assisted Self-Interview (ACASI)? How well do these responses correlate with mycobacteriology and radiology?

3) What is the best timing for nasopharyngeal swabs for evaluating AMR in patients who receive a course of antibiotics during TB investigations?

4) In the standard of care setting, what proportion of adult patients presenting to primary care centres with cough for at least 2 weeks experience the following adverse outcomes (as defined under the clinical benefit composite endpoint)?

- **a.** death
- **b.** hospitalisation
- **c.** missed TB diagnosis
- **d.** HIV care loss to follow up
- **e.** TB care loss to follow up

5.1 Specific objectives of the pilot study

1) To determine the proportion of adults with prolonged cough who

a. present to primary care having already had antibiotics for the index clinical complaints.
b. receive antibiotics before sputum mycobacteriology results at first presentation
c. receive antibiotics after negative mycobacteriology

2) To establish an objective way of documenting response to antibiotic treatment using Audio Computer Assisted Self Interview (ACASI). Assessing ACASI responses against clinical signs, outcomes of TB mycobacteriology and chest radiography.
3) To determine:
    a. the prevalence of *Streptococcus pneumonia*;
    b. the prevalence of resistant *Streptococcus pneumonia* isolates;
    c. the optimal specimen collection timing for evaluating impact of antibiotic use on prevalence of *Streptococcus pneumonia* isolates resistant to common antibiotics
4) To establish standard of care rates of the following adverse clinical outcomes:
    a. death
    b. hospitalisation
    c. missed TB diagnosis
    d. HIV care loss to follow up
    e. TB care loss to follow up

5.2 Population for the pilot study

This exploratory study will include up to 400 adult (≥18 years old) patients presenting to primary care centres with cough for at least 14 days. We will exclude patients not meeting the eligibility criteria of the clinical trial.

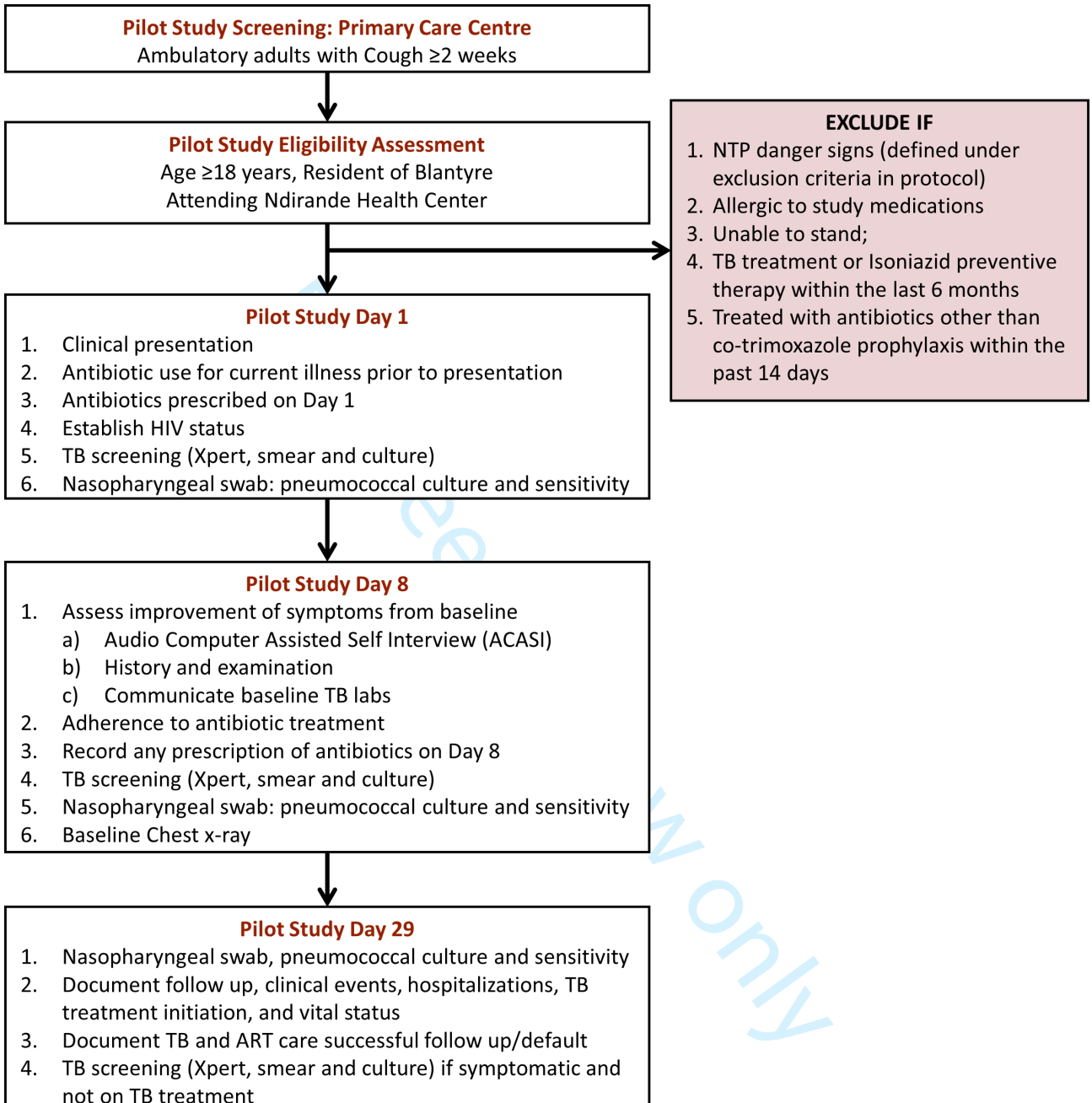
5.3 Pilot study procedures

The pilot study procedures are outlined in the flow chart below. Following pilot study informed consent, we will use a baseline assessment questionnaire to collect clinical history, and antibiotic use for the index illness prior to the clinic visit. Throughout follow up, we will record all antibiotic use from any source. We will collect sputum samples for mycobacteriology from all participants on Day1 and Day 8.

We will establish HIV and TB diagnosis throughout the study, link participants to care services, and follow their adherence to follow up. For TB we will use a combination of Xpert, smear and culture on Day 1, 8 and whenever symptomatic suggestions of TB arise. We will also perform a chest x-ray on Day 8 and a follow up film on Day 29.

We will collect nasopharyngeal swab samples, for antimicrobial resistance assessment using *Streptococcus pneumonia* culture and sensitivity, on Day 1, Day 8, and Day 29. We will assess change in symptoms and well-being from Day 1 to Day 8, by using various combinations of questions and answers delivered via Audio Computer Assisted Self Interview (ACASI) on Day 8. We

will ask participants which sets of questions they found easy to understand. We will also collect clinical information on all study visits including illness events, hospitalisations and vital status.



Pilot study flow diagram, summarizing the study procedures at each visit.

5.4 Data analysis

We will report the proportions of participants who used any antibiotics prior to primary care and during work-up for Tuberculosis. We will determine the best ACASI question and response combinations by participant reported ease of use, and by assessing correlation with clinical findings,

mycobacteriology and radiological outcomes. The optimal time for assessing AMR will be determined by comparing incidence of resistant *Streptococcus pneumonia* isolates at days 8 and 29.

We will comparing participants exposed to antibiotics to those not exposed to antibiotics by estimating and reporting relative risk and 95% confidence intervals for:

1) Day 8 and Day 29 of resistant Streptococcus pneumonia
2) Composite adverse outcome of experiencing any of: death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up

6 Study procedures

6.1 Screening

At the designated primary health care centres, study staff will approach patients with symptoms of pulmonary tuberculosis (including cough of any duration, fever, weight loss, and night sweats) with information about the study. Those willing to be screened for eligibility will be assessed against the study inclusion and exclusion criteria.

6.2 Informed consent

We will seek written informed consent (Appendix 1) from all patients who meet eligibility criteria before any trial-specific procedures. Screening for tuberculosis symptoms will not be considered as part of the study procedures, as it is already a fundamental component of the routine clinical assessment and history taking. A member of the study team will hand an informed consent form to a potential participant in their preferred language (Chichewa or English) detailing background, procedures, risks, benefits and participant expectations should they choose to join the study. The consent form will also state that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and no obligation to give reason for the withdrawal.

If they choose to join as a study participant, we will then request them to sign two copies of informed consent form. If a potential participant does not know how to read or write, we will perform the informed consent process in the presence of a witness. In such cases, if they agree to participate in the study, we will ask them to sign using a thumb-print in the presence of their witness and a study team member. We will keep one copy of the signed informed consent forms and hand the participant the other copy.

6.3 Baseline procedures

After consenting, we will on the same visit request participants to provide 2 on the spot sputum samples for smear microscopy, Xpert and culture collected at least one hour apart. Those unable to spontaneously produce sputum will be instructed in the physiotherapy manoeuvre of “huffing” (forced expiration technique) for inducing mucus clearance from the airways.

Patients still unable to provide at least one mucoid sputum sample of >1 ml will initially will be given a sputum container and asked to return it the next day. If they do not manage to produce sputum at home, their mycobacteriology results will be treated as missing. We expect ~15% of participants to fall in this category[31] and have accounted for them in the sample size estimation. For participants who produce less than the needed quantity of sputum, we will process them for the planned tests in the following priority order: 1) Xpert MTB/RIF, 2) MTB culture, 3) smear microscopy. The Xpert MTB/RIF

is the single most important guide for immediate clinical diagnosis and the MTB culture is the single most accurate reference diagnostic.

We will also collect a urine sample which we will store for subsequent lipoarabamannan antigen detection (LAM); and a nasopharyngeal swab for pneumococcal culture and sensitivity testing to estimate prevalent antimicrobial resistance. We will also perform HIV tests according to the national algorithm, and if positive we will do HIV viral load. After completing all Day-1 visit procedures, we will link the newly tested positive participants to routine HIV care and will document when they start ART (Malawi National Program provides same-Day-ART initiation to all newly-diagnosed or untreated HIV-positive patients). After the sample collections, we will collect the following information:

- Demographic data, including precise geographic locator information using ePAL geolocation software (to aid follow-up). The locator information will also include phone numbers for the participant and for up to 3 family, or friends they nominate as alternative contacts.
- Clinical history including information on tuberculosis symptoms and health care seeking for HIV and tuberculosis care services including ART, cotrimoxazole, isoniazid preventive therapy, and past TB treatment.
- Vital signs including height and weight

After completing all these baseline procedures, we will randomise the participants to the three study arms.

6.4 Assignment of interventions

Step 1: An independent statistician based at LSHTM and without contact with participants or the study staff that see participants, will use the ralloc command in Stata (StataCorp LLC, College Station, Texas USA. Release 15.0) to prepare a random allocation sequence in advance of study recruitment efforts. Randomisation will be 1:1:1 to the three arms of the trial, block-randomised with variable block sizes, and stratified by primary care centre.

Step 2: Each treatment allocation will be printed alongside a randomisation number onto a pdf document.

Step 3: The statistician will email the pdf document to an independent designee within university of Malawi who will print and place the randomisation assignments in envelopes labelled with randomisation numbers. The independent designee will hand the envelopes directly to the study pharmacist who will also receive a shipment of study medications. The pharmacist will store the envelopes in a secure location within the pharmacy.

Step 5: The pharmacist will pre-pack 625 each of protocol doses of azithromycin and amoxycillin without any reference to the allocation sequence. There is no need to refer to the allocation sequence for this step because the dosage for both treatments is the same and the total number of allocation for each treatment is known.

Step 6: At the beginning of each working week and upon request from study site, the study pharmacist will hand to site coordinators of each primary care center, a recruitment-rate-driven daily working stock of 1) the sequentially numbered sealed opaque envelopes containing randomization numbers and corresponding treatment allocations, and 2) study drugs.

Step 7: Study staff from each site will conduct patient eligibility assessments. Patients meeting the quick criteria of age and cough for ≥14 days, will be assigned screening IDs before being taken through the full eligibility criteria and consenting process. Participants will be considered eligible and ready for randomisation after they meet all criteria and sign consent.

Step 8: Upon signing consent, the participant will be taken to the site-coordinators (nurse or clinical officer) who will assign them the next available study ID number and document it on their paper and electronic eligibility checklist and enrolment CRF. The study ID number will be the number on the treatment allocation envelope plus a site-specific code. They will then open the envelope, document the treatment assignment, to the participant's enrolment paper and electronic case report forms as well as on a study card that will be pasted in the participant personal health profile book.

Step 9: The coordinator will double-check to ensure that the enrolment number and the treatment assignment are recorded correctly. They will then record screening date, screening ID, randomisation date, study ID, and randomisation arm on an enrolment log. They will then administer the allocated treatment. Administering study medications will not be considered as prescribing considering that prescription to all eligible participants will have already been done by the study protocol.

Step 10: When the stock of either envelopes or study drugs runs out,, the nurse-coordinators will reorder a from the study pharmacist.

Additional details

All steps of receipt, and utilization of the allocations and study drugs are elaborated in a detailed SOP. The SOP guides implementation of the above plan as far as possible and in line with site conditions.

The study drugs will be pre-packed blindly without any reference to treatment allocations ensuring that neither the pharmacist nor the nurse-coordinator know the treatment allocations until just before assigning to a participant.

6.5 Blinding

We will mask the treatments as far as possible. The study pharmacist will remain blinded as they will use the randomly- allocated label numbers to prepare and pack the correctly dosed study medications in opaque packaging. Study outcome assessment will occur without reference to study treatment allocation. All laboratory forms for mycobacteriology and nasopharyngeal pneumococcal work will have no reference to participant treatment allocation. On Day-8, assessment of improvement from baseline symptoms will utilize audio computer-assisted self-interview (ACASI) to minimise potential for social-mediated reporting and ascertainment biases (see Procedures Section of the protocol). All clinical endpoints assessment case report forms will bear no reference to treatment arm. However, we will keep participants, research coordinators, and routine care staff unmasked to ensure safety of the participants and allow appropriate patient management decision-making which may be related to the trial interventions.

6.6 Participant follow up

Following enrolment and completion of baseline procedures we will ask participants to return for follow up visits on days 8, and 29. They will be given 1 sputum collection bottle when leaving the clinic on Day-1 to bring with them sputum for mycobacteriology planned for Day-8 ("morning" specimen) followed by collection of one further "spot" sputum on Day-8, 2 sputum samples in total). We will also collect a second urine sample for storage for subsequent LAM antigen testing. Patients unable to produce at least one mucoid sputum sample of >1ml on Day-8 will be assumed for purposes of analysis to be mycobacterially negative for the Day-8 sputum samples. We are performing two sets of sputum examinations (Day-1 and Day-8) for each participant to strengthen the accuracy of the reference standard. Considering that TB progresses very slowly, making a diagnosis on Day-8 is not different from that made on Day-1.

We will advise participants that their sputum TB test results will start becoming available from 48 working hours after collection, but with the last test (MTB culture) taking up to 4 weeks. Patients will be advised that they will not be routinely contacted if positive TB test results become available before their Day-8 appointment (as is standard for outpatient management without danger signs in Malawi), and so will be advised to report promptly back to the clinic (with refund of transportation given) if they experience any clinical deterioration during Days 2 to 7.

In the circumstances where TB treatment is commenced before completion of antibiotics prescribed for trial-of-antibiotics (amoxicillin and azithromycin), we will ask them to carry on with their allocated intervention together with the TB treatment.

6.6.1 Day-8 activities

On Day-8, the first activity before the participants undergo all other evaluations will be documentation of self-reported improvement of baseline (Day 1) TB symptoms using a pilot-validated set of questions and answer options delivered via Audio Computer Assisted Self Interview (ACASI). We will use ACASI with the goal of eliminating inter-observer variability and patient/interviewer reporting or ascertainment biases. After a "how to use" orientation and testing session, the participant will be left alone in the room to interact with the computer. A pre-recorded interviewer will ask the participant questions related to how their symptoms have changed on that day compared to how they were on Day-1 and will offer categorised voice-recorded responses with touch screen response buttons. The ACASI questionnaire will also include questions about adherence to study arm drugs and any other medical care (including traditional medicine) sought during the previous week.

Other activities for all participants on Day-8 include:

- collection of a second sputum sample for mycobacteriology tests.
- providing participants with Day 1 smear and Xpert results linking those with positive tests, ongoing symptoms and other illnesses with routine care for appropriate management.
- clinical history detailing clinical events since enrolment.
- documentation of any medications including antimicrobials and traditional medicine outside the study
- providing a study Day-29 appointment card

For participants with negative Day-1 mycobacteriology results we will perform clinical evaluation after ACASI and will inform the patient that any positive Day-8 sputum mycobacteriology results will be reported actively (via telephone or house visit) as soon as quality-assured results become available (within 48 working hours for microscopy and Xpert). Patients who have not had complete resolution of symptoms will be referred with all available results to routine primary care management.

6.6.2 Day-29 activities

Day-29 will be the final study visit. We will on this visit, collect data on clinical impact of antibiotic treatment and risk of AMR. In line with the second primary endpoint (composite clinical impact), we will document:

1) vital status
2) hospitalisations
3) identify missed TB diagnosis by using culture results from Day 1 and Day 8 sputum, any chest X-rays performed in follow up, and repeat mycobacteriology if symptomatic
4) perform HIV tests for those with unknown status and eligible for routine HIV test.
5) establish the status of HIV care and follow up
6) establish the status of TB care and follow up

We will first collect information on clinical events prior to and at the visit and communicate all available sputum culture results and the final reported CXR results.

After collecting the clinical information, we will collect nasopharyngeal swab sample for assessing antimicrobial resistance. To collect the sample, a trained study staff will swab the participants' nasopharynx and place the swab in a tube containing skim milk tryptone glucose glycerol (STGG).

6.7 Laboratory methods

6.7.1 Tuberculosis mycobacteriology

We will process mycobacteriology tests at the Malawi College of Medicine TB laboratory, a reference laboratory located in Blantyre. For sputum samples collected on Day-1, we will perform smear microscopy, Xpert MTB/RIF and MTB culture. For sputum samples collected on Day-8, we will perform smear microscopy and MTB culture. We will use Mycobacteria Growth Indicator Tube (MGIT) and Lowenstein-Jensen (LJ) culture methods for TB culture. Once isolated, we will perform speciation as *Mycobacteria tuberculosis* (MTB) or non-tuberculous mycobacteria (NTM) using MBP84 antigen testing, microscopic cording and, if necessary, morphology and growth characteristics at different temperatures and on solid (LJ) media containing p-nitrobenzoic acid (PNB).

6.7.2 Urine antigen testing for lipoarabamannan and other MTB antigens

Urine will be collected and stored as two 1 ml aliquots at -20°C from each participant on both Day-1 and Day-8 for subsequent mycobacterial antigen testing. No appropriate product is available for immediate use, but we anticipate that a commercial product with sufficiently high analytic accuracy for use in ambulant outpatients (sensitivity and specificity) may become available during the course of, or soon after, the study. If ongoing evaluations of the FIND-sponsored FujiFilm product[45] meet or exceed pre-specified requirements for clinical utility in the outpatient context, then point-of-care LAM testing at Day-1 and Day-8 will be added to the mycobacteriological definition of TB and patient management as soon as kits have been obtained and evaluated in Malawi.

6.7.3 Antimicrobial resistance testing

We will store swabs in STGG at minus 80°C. At a later stage we will thaw them in batches, and plate them onto selective media and culture colonies consistent with *S. pneumoniae*. We will determine Minimal inhibitory concentrations (MICs) using E-test strips (azithromycin and amoxicillin), and Kirby Bauer Disc diffusion testing (azithromycin, rifampicin, tetracycline, ceftriaxone, chloramphenicol, co-trimoxazole, erythromycin and penicillin) and define resistance by EUCAST breakpoints.

We will store isolates and remaining STGG at minus 80°C to allow genotypic characterization, isolation and susceptibility testing of other key respiratory pathogens, FTD 33 respiratory pathogen diagnostic panel, metagenomics analysis, and microarrays to detect multiple carriage and macrolide resistance genes in a broader range of pathogens at a later stage.

6.8 Loss to follow-up

To minimise loss to follow up, we will at enrolment record geolocation information of participants' place of residence using ePAL android app, a high-resolution mapping system validated in Blantyre. We will also record up to 3 contact phone numbers of the participant and their nominated friends and relatives. Should a participant miss a study visit, we will contact them by phone or by visiting them at home to encourage them to attend the study visit before expiry of prescribed visit window.

We anticipate a loss to follow-up of 5% by Day-8, and 10% by Day-29. We have accounted for these assumptions in the sample size calculation. We will not replace participants who discontinue study participation or study treatment regardless of reason for withdrawal or discontinuation or the time either of these occurs.

6.9 Trial closure

We will consider the trial closed after completing follow up of the last enrolled participant, and upon recording all mycobacteriology laboratory reports. Antimicrobial resistance lab work will continue beyond trial closure. The trial may be terminated early by the trial steering committee upon recommendation of the DSMB. The halting rule for a trial arm is an unacceptable high level of deaths assessed using an alpha determined at the first DSMB meeting.

6.10 Summary schedule for study procedures

In Table 6 below, we have summarised all key study procedures over the study period.

Table 6: key study procedures over the study period

	STUDY PERIOD			
	Enrolment	Follow up		
TIMEPOINT**	**Day-1**	***Day-8***		***Day-29***
ENROLMENT:				
Eligibility screen	X			
Informed consent	x			
Allocation	x			
INTERVENTIONS:				
Azithromycin	x			
Amoxicillin	x			
Standard of care	x			
ASSESSMENTS:				
Demographics	x			
History of antibiotic use	x	x		x
**History & examination*	x	x		x
***Sputum collection*	x	x		
Urine for TB LAM test	x	x		
Nasopharyngeal swab	x			x
HIV test and CD4 count	x			x
Linking to routine care	x	x		x
[1]*ACASI*		x		
***Clinical events*		x		x
Update contact & address		x		x

*For symptomatic participants, Day-8 sputum mycobacteriology should be fast-tracked to inform care before they leave the clinic. Chest X-ray should be performed and interpreted in real-time.

**Give sputum bottles at end of Day-1 visit for submission on Day-8. Also collect sputum and perform mycobacteriology at any time of the study when clinically indicated

***Illnesses, clinic visits, radiological outcomes, new HIV diagnosis, new TB diagnosis, death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up

[1]Audio Computer Assisted Self-Interview for documenting change of symptoms on Day- 8 versus Day-1

7 Safety reporting

7.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product.

7.2 DMID grading for AEs

We will adopt the events grading criteria prepared by the Division of Microbiology and Infectious Diseases (DMID) of the USA National Institutes of Health as shown in the table below.

1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
Transient or mild discomfort (< 48 hours); no medical intervention required	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention required	Marked limitation in activity, some assistance usually required; medical intervention required, hospitalizations possible	Extreme limitation in activity, significant assistance required; significant medical intervention required, hospitalization probable

7.3 Grading for expected events

The following table provides guidance for grading known important or frequent side effects of azithromycin (based on the AE grading criteria provided in the BREATHE Trial Protocol, also investigating azithromycin) and amoxicillin graded on the DMID scale. All events not mentioned here or in Appendix 2, will be graded using the DMID grading for AEs table presented above.

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
Side-effects	**1**	**2**	**3**	**4**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal oedema
Rash ***Specify type, if applicable***	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Mental state changes	mild anxiety or depression	moderate anxiety or depression; therapy required;	severe mood changes requiring therapy; or suicidal ideation;	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
		change in normal routine	or aggressive ideation	
Photosensitivity	Painless erythema covering <10% body surface area	Tender Erythema covering 10 - 30% body surface area	Erythema covering >30% body surface area and erythema with blistering, requiring intervention	Life-threatening consequences; urgent intervention indicated
Arrhythmia (by ECG or physical examination) ***Specify type, if applicable***	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Prolonged QTc Interval	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Nausea	Transient (< 24 hours) or intermittent AND No or minimal	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration	Life-threatening consequences (e.g., hypotensive shock)

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
	interference with oral intake		indicated (e.g., IV fluids)	
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Laboratory	**1**	**2**	**3**	**4**
ALT or SGPT, High ***Report only one***	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Creatinine Clearance or eGFR, Low ***Report only one***	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed

7.4 Causality

When reporting on serious adverse events, the trial investigator will state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship. They will also state whether the adverse event was expected and what if any action was taken.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.5 Reporting Procedures

7.5.1 Non-serious Adverse Events (AEs)

Adverse events will be ascertained from patient follow-up visits or reports from relatives or guardian if patient cannot be contacted for follow-up. Study clinicians will be responsible for recording of details of the event including a description of the event, date of onset, severity, assessment of relatedness to trial interventions. Adverse events will be recorded in case report forms and uploaded into the study database.

7.5.2 Serious Adverse Events (SAEs*)*

All serious adverse events (SAEs) will be recorded on the relevant study CRFs and reported immediately to the Principal Investigator who will ensure that they are compiled in aggregate form and reported to COMREC and the DSMB once every 6 months. The DSMB will review SAE reports at their 6 monthly meetings and issue recommendations which will be shared with ethics committees. Events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition will not be reported as SAEs.

8 Economic evaluation

8.1 Objective

The objective of the economic evaluation is to undertake a cost-utility analysis to estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other. We will systematically compare costs and consequences associated with the interventions.

8.2 Outcomes

We will perform a within trial comparison of the three treatment arms to estimate the incremental cost per quality-adjusted life year (QALY) gained for the azithromycin or amoxicillin arm in comparison to standard of care. Costs will be estimated from the Malawian Ministry of Health perspective. Health outcomes will be quantified in QALYs, estimated from participants' responses to the Chichewa version of the EQ-5D-3L, a Health quality of life (HRQoL) measure.[46,47] We will adopt a time horizon matching the length of participant follow-up to achieve the within trial evaluation.

8.3 Data collection

The health economic data collection will be undertaken alongside planned clinical data collections. We will administer the Chichewa version of the EQ-5D-3L to all trial participants at baseline (Day1), Day 8 and Day 29. The Chichewa EQ-5D-3L was prepared in accordance with international and EuroQoL guidelines. The EQ-5D uses a descriptive system and a visual analogue scale (VAS). HRQoL on the day of response is defined using the descriptive system in terms of the following dimensions: 1) mobility, 2)self care, 3)usual activities, 4)pain/discomfort, and 5) anxiety or depression. The responses are then split into the following ordinal levels: 1) no problems; 2) some or moderate problems; and 3) severe or extreme problems.

The EQ-5D has 243 health states to which each response is allocated and converted to an EQ-5D utility score using a tariff. Tariff sets are derived from national surveys and currently no Malawian EQ-5D tariff exists. Zimbabwe, a setting similar to Malawi, has EQ-5D tariff set. In this study, we will use the Zimbabwean set to derive EQ-5D utility scores[48] an acceptable practice considering the similarities in how the two populations value health.[49] The EQ-5D utility scores in the Zimbabwean tariff, range from 1.0 (which means no problems in the five dimensions) to -0·29 (defined as severe problems in all five dimension).

We will capture all healthcare resources used by trial participants from recruitment into the trial till Day 29. This will be undertaken on Day 1, Day 8 and Day 29. Healthcare resources will be translated into direct medical costs using previously estimated costs[47,50,51] and the wider literature.

Drug prices will be based on International market prices.[52] The health resource use questionnaire will at a minimum capture:

- Outpatient clinic visits
- Days of inpatient hospital care
- Medications
- Investigations and procedures

8.4 Data analysis

Our primary analysis will focus on direct intervention and the broader healthcare costs. We will define direct intervention costs as the costs associated with the application of the interventions. We will plot health state values measured by the EQ-5D-3L against time assuming that the health states reported at each time point are linearly connected. We will estimate QALYs associated with participant health profile by area under the plotted curve as calculated using the trapezium rule.

We will use a range of analytical methods depending on whether baseline covariates (EQ-5D utility values) are balanced between the trial arms or not. If they are balanced, we can obtain unbiased cost-effectiveness estimates by using non-parametric bootstrap approaches; if imbalance exists regression methods will be the approach of choice.

We will explore a range of estimators and undertake model diagnostics to determine the optimal model because the distributions of costs and QALYs are commonly skewed, often bimodal, or truncated. We will estimate mean costs and outcomes for each intervention together with respective mean incremental cost-effectiveness ratio. We will for each estimate report respective measures of uncertainty (standard errors and confidence intervals). We will also estimate the net monetary benefits (NMBs) for a range of different willingness to pay (WTP) thresholds. To identify the optimal intervention at different WTP thresholds, we will construct cost-effectiveness acceptability curves (CEACs) based on the NMB framework.

8.5 Missing data

For each participant we will collect complete data as far as possible but in cases of missing values, a common occurrence in trials, we will perform additional analyses to explore the impact of and account for the missingness.

9 Data management

9.1 Source Data

We will consider a document as source if it is where data were first recorded, and from which we obtained participants' case report forms (CRF) data. These will include hospital records, health center records, participant health passport, laboratory and pharmacy records, diaries, radiographs, and correspondence. We will consider CRF entries as source data if the CRF is the site of the original recording.

We will on all study-specific documents, other than study ID code list, the signed consent forms household locator form and, refer to the participant by their trial participant identification number, not by name. We will keep study ID code list, consent and locator forms separate from the rest of the participant file to avoid linkage between participant name and the study ID.

9.2 Data collection methods

We will collect data using standardised, pre-tested CRFs in two forms:

- programmed into android tablets using Open Data Kit (ODK) platform (opendatakit.org) with paper back-ups.
- optical mark recognition readable forms read and extracted using TELEFORM system (Cardiff Software, Inc., Vista, CA), an optical-character-recognition software.

9.3 Data management

Any participants' identifiable data collected by the Study Coordination Centre will be stored securely and their confidentiality protected in accordance with the Data Protection Act 1998.

To ensure data security and maintenance of participant confidentiality, we will take several strict measures. All the study data collection tablets and computers will be encrypted, password protected and stored in a fireproof lockable cabinet inside a locked room. The principal investigator, study coordinator and data manager will be responsible for the maintenance of the tablets as well as all other computers, and their security from viruses and theft. All users will check in with the study coordinator and sign for data entry tablets every time they are taken out to for data entry and upon return. Whenever not in use, the devices will be kept in their locked cabinet.

We will keep all paper records in a locked space only be accessible to the principal investigator, co-investigators and delegated study staff. Study databases will be encrypted, password protected and will be stored on dedicated servers within the University of Malawi College of Medicine. We will keep all electronic and paper records securely for up to 10 years after the end of the trial in accordance with LSHTM Records Retention & Disposal Schedule guidelines.

9.4 Quality control and quality assurance

We will apply quality control at each stage of data handling in accordance with GCP requirements to ensure that all data are reliable and have been processed correctly. We will manual review all paper CRFs for completeness, accuracy and legibility before scanning. Our ODK data entry system will include automatic pre-programmed real-time data validation. The TELEFORM system will also have pre-programmed automatic data validation capabilities. We will perform data quality assurance (QA) on a random 10% of all participant files. The QA process will involve examining database entries and for paper source documents, verification of database entries and source.

9.5 Access to data

We will upon request, provide direct access to authorised representatives from the Sponsor, host institution and the regulatory authorities to allow smooth running of trial-related monitoring, audits and inspections.

10 Data monitoring and quality assurance

10.1 Data monitoring

Site monitoring for safety will be conducted to ensure human subject protection. The study will be monitored just before commencing enrolment, then once every 6 months by a monitoring team from the University of Malawi College of Medicine. The objective will be to ensure that study procedures, study products administration, and data collection processes are of high quality and meet ethical and regulatory guidelines. The regular monitoring will focus on the following areas: 1) protocol adherence, 2) informed consent documentation, 3) trial endpoints, 4) treatment discontinuation, 5) regulatory documents, 6) compare source documents and case report forms for accuracy, and 7) documentation practices in general.

10.2 Audits and Inspections

The study will be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

10.3 Data Safety and Monitoring Board (DSMB)

We will set up a DSMB before commencing trial activities. The DSMB will provide independent review of the study conduct, progress and findings. It will comprise 3 members including a chairperson who will be responsible for collating and communicating the views of the DSMB. The DSMB will consist of an independent statistician and two clinicians, at least one of them a physician, with research experience and expertise in the management of tuberculosis and HIV in Africa. The proposed data safety monitoring plan will be discussed in a teleconference including the DSMB members and the key investigators prior to the study starting.

The proposed meeting schedule is 6 monthly. Two weeks before a 6 monthly DSMB meeting, the study team will prepare a report covering study progress, study approvals, any obstacles, and recruitment statistics, adverse events, withdrawals and trial outcome measures. The DSMB will, through its chairperson, provide written feedback to the principal investigator who will be responsible for passing it on to ethics committees.

10.4 Trial Management Group (TMG)

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-Day-management of the trial will be co-ordinated through the University of Malawi College of Medicine.

10.5 Trial Investigational Team

Our investigational team includes expertise in diagnosis and management of TB; clinical evaluation of TB diagnostics; design and conduct of large randomised controlled trials; laboratory TB and AMR diagnostics; data management and analysis.

Chief investigator

Dr Titus H Divala: the chief investigator and PhD student will be responsible for protocol development, coordination and conduct of the trial, governance, data management, data analysis and results dissemination. Dr Divala is a clinician with a career interest in clinical trials. Apart from medical training, he holds MPH and Masters of Science in epidemiology and preventive medicine. He has managed two large GCP, US-NIH-funded clinical trials, one of which was IND as the local PI supervising over 40 study staff at two sites in different cities. He has worked as a clinician for over 8 years in Malawi, a period when identifying TB cases and putting them on treatment was a daily job. This topic therefore falls in area of great personal interest above and beyond the potential benefit it has towards improving patient care in Malawi and all low and middle-income countries where 95% of the TB burden lies, where this approach is the standard.

Co-investigators and members of PhD supervisory team

Prof Katherine L Fielding: a seasoned TB statistician and clinical trialist, and PhD supervisor for the CI, will be responsible for protocol development, conduct of the study, and data dissemination.

Prof Elizabeth L Corbett: a seasoned TB clinical epidemiologist and PhD co-supervisor for the CI, will be responsible for protocol development, conduct of the study, and data dissemination.

Co-investigators and members of PhD advisory committee

Dr Derek J Sloan: clinician with detailed local clinical and research experience, will be responsible for protocol development, trial implementation and data dissemination.

Prof Neil French: a seasoned pneumococcal expert, will be responsible for protocol development, oversee all aspects of AMR work, and data dissemination.

Collaborators

Dr Marriott Nliwasa: clinician, with experience conducting studies in the study setting. He will be support the conduct of the study, linkage with the national program, and data dissemination.

Mr Augustine Choko: statistician, with expertise and experience in using ACASI. He will support ACASI development, data management and development of analysis plan.

Dr Ankur Gupta-Wright: clinician, will provide clinical input in protocol development and clinical consultation support to research coordinators during study implementation..

Dr Jennifer Cornick: microbiologist, will be support protocol development, and AMR laboratory methods and analysis, and data dissemination.

Prof Jon Øyvind Odland: Epidemiologist and honorary professor at University of Malawi College of Medicine, responsible for seeking ethical approvals from the funder appointed ethics committee.

11 Ethics and dissemination

We will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki and in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6 (R2) of November 2016.

11.1 Risk assessment

This is a low risk study as it is using already licensed antibiotics with good safety profile in a population defined by national clinical guidelines as clinically stable and not requiring other intervention but TB investigations. Our work complements standard of care by bringing in detailed TB diagnostics. In our study, the standard of care equivalent of the antibiotics we will prescribed on Day-1 to those randomised to either azithromycin or amoxicillin arms, are in standard of care prescribed on Day-8 only to mycobacteriology negative symptomatic patients (similar to the no antibiotic or standard of care arm of our trial). So, participants randomised to no antibiotic at Day-1 will not be receiving inadequate care but the recommended standard management of withholding antibiotics until after the TB results are available (Figure 1). To maintain participant safety and continuity of their care while on study interventions, we will not blind routine care clinical team and they will be free to manage the participants on their clinical judgement and national guidelines.

11.2 Research ethics approval

We will seek ethical approval for the trial protocol, informed consent forms, participant information sheet, any advertising material, and amendments to any of these documents, from the University of Malawi College of Medicine Research and Ethics Committee (COMREC), the LSHTM Research Ethics Committee, and Regional Committee for Health and Research Ethics, NTNU-Midt, Norway (on behalf of the funder). We will seek regulatory approval from the Malawi Pharmacy, Medicines, and Poisons Board (PMPB). Every year when the trial is active, we will seek continuous ethical review and approval before expiry of previous year's approval. In the event of an amendment, the changes will only be implemented upon ethical and regulatory approval.

11.3 Indemnity

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.4 Sponsor

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.5 Declaration of interests

The study team declares that they have no conflict of interest in conducting this clinical trial.

11.6 Cost of participation, ancillary and post-trial care

During the study, participant will benefit from frequent interaction with clinical study staff and associated optimised management of illnesses. There are minimal risks including discomfort associated with collection of nasopharygeal samples, and side-effects of study interventions. We will reimburse participant transport for attending study visits.

11.7 Dissemination policy

This work will form part of a PhD thesis for Titus Divala, which he will submit to the London School of Hygiene & Tropical Medicine (LSHTM). All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator.

Members of the TMG and the DSMB will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy

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13 Appendix 1: Informed consent

Included as a separate document on headed pages.

14 Appendix 2: Division of Microbiology and Infectious Diseases (DMID) adult toxicity table

TABLE VERSION: November 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal LLN = Lower Limit of Normal R_x = Therapy Req = Required

Mod = Moderate IV = Intravenous ADL = Activities of Daily Living Dec = Decreased

- **ESTIMATING SEVERITY GRADE**

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 Mild Transient or mild discomfort

(< 48 hours); no medical intervention/therapy required

GRADE 2 Moderate Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 Severe Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 Life-threatening Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THIS TABLE

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide for Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/d L	8.0 - 9.4gm/dL	6.5 - 7.9 gm/d L	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/ mm^3	750-999/ mm^3	500-749/ mm^3	<500/ mm^3
Platelets	75,000-99,999/ mm^3	50,000-74,999/ mm^3	20,000-49,999/ mm^3	<20,000/ mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 / mm^3	15,000-30,000/ mm^3	>30,000 or <1,000 / mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ ml	41-50 mcg/ ml	51-60 mcg/ ml	> 60 mcg/ ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/l	> 7.0 mEq/ L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/d L or abnormal glucose *with* mental

				status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/d L or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/d L	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/d L	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN

increase in other liver function test)				
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/d L	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
EN ZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day

Hematuria	microscopic only \<10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion
CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment

Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused
RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy
GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4

Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/Day-or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/Day-or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink flu ids; requires IV fluids
NEUROLOGICAL				

	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at	sensory loss involves limbs and trunk; paralysis; or seizures

	focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	ankles) and/or joint position or mild impairment that is not symmetrical	least mod degree in multiple different body areas (i.e., upper and lower e xtremities)	
MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no	muscle	severe muscle	frank

	limitation of activity	tenderness (at other than injection site) or with moderate impairment of activity	tenderness with marked impairment of activity	myonecrosis
SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	

Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

15 Appendix 3: Package insert for Azithromycin and amoxicillin

Included as separate attachments.

PARTICIPANT INFORMATION SHEET

Participant information sheet

What is the benefit and unintended consequences of using antibiotic treatment as a way of excluding tuberculosis disease in patients with cough?

Introduction

We would like to invite you to take part in a research study. Joining the study is entirely up to you. Before you decide, you need to understand why the research is being done and what it would involve. One of our team will go through this information sheet with you, and answer any questions you may have. Ask questions if anything you read is not clear or you would like more information. Please feel free to talk to others about the study if you wish. Take time to decide whether or not to take part.

What is the purpose of the study?

Tuberculosis (TB) is a disease that causes a long illness and cough with sputum. Although curable TB is difficult to detect. When they fail to detect TB after testing sputum, clinicians give antibiotic treatment that can cure all other causes of TB symptoms but not TB. In this approach, TB is considered ruled out if patient gets better and it is considered likely if they do not get better. The goal of this research study is to develop understanding of how well the antibiotics help distinguish TB patients from those who do not have it, whether giving antibiotics carries other health benefits, and whether it leads to development of disease causing organisms which are resistant to drugs.

We will learn about this by comparing a group of patients given antibiotics on the first day of the study to another group not given antibiotics. There will be two groups receiving antibiotics as follows: 1) Azithromycin taken as one tablet once a day for 3 days, and 2) Amoxicillin 4 capsules taken three times a day for 5 days. The group you will go into, out of the three, will be decided by chance so you can fall into any group.

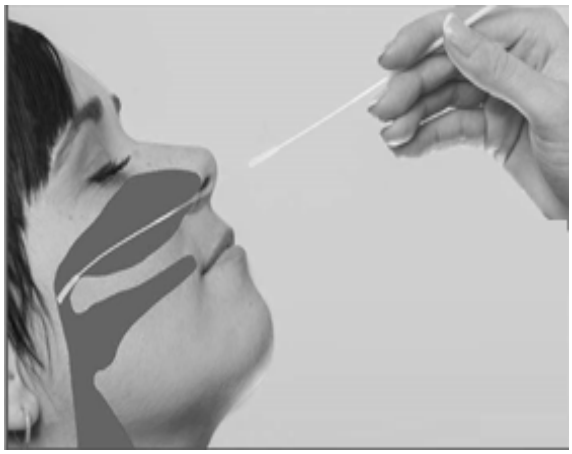
What will be involved if I accept to participate in the study?

We are considering you for participation in this study because you told us that you have a cough. Any patient who has been coughing for at least 2 weeks, is at least 18 years, and lives within Blantyre, is eligible to participate in this study if they do not have signs consistent with serious illness. Apart from you, we will recruit 1,874 other individuals.

Study activities will be performed the first day, at 1 week (Day 8), and at one month (Day 29). At each of these study visits, we will ask you questions about your contact details, your health, use of medications, and any illnesses or hospitalisations you may have had in between study visits. We will also document relevant details from your health passport and other clinical documentation you may have.

On Day 1 and at 1 week, we will ask you to submit sputum and urine samples for TB tests. If you are not able to give sputum on Day 1, we will give you containers so that you can bring them the following morning. Some of the sputum TB tests results will become available after 7 days and we will pass them to health center clinicians who will make a plan for your care, the other results may take up to 4 weeks so you will get them at the 1 month visit. Urine TB test results will not be available for your clinical care.

We will also do an HIV test. If the results are confirmed to be HIV positive we will do a viral load test, and at the end of the study activities on Day 1, we will link you to HIV management team here at the health center who will start you on treatment. Should we make a diagnosis of TB or HIV at any other point during the study, we will link you with the responsible health center team for treatment services.



On day 1 and at 1-month visit, we will swab the back of the inside of your nose as shown in this picture to collect germs that live there. We will test the germs for drug resistance. Results of this test are not relevant to your care.

On 1-week visit, we will ask you to report how your health has changed in comparison to how you were on day 1. These questions will be read to you by a computer and you will answer them by choosing various options which it will display during the interview.

The 1 month visit will be the final study visit where we will also provide you with results for TB culture and ask if you have TB symptoms. If you are in HIV or TB care, we will ask how your follow up is going. The appointment with you at 1 months is very important because it will help you to know the results of the TB tests and it will also help us know the status of your health.

The number of clinic visits you will make for this study is at least three. Here we count Day 1, one visit after one week, and another visit at one month. If you have not been able to come here for any of the visits, we will remind you by phone call or we will use the permission and information you will give us to visit you at your home. The first visit will take about 60 minutes and the later visits will take about 30 minutes each.

Will there be any risks involved in this study?

This study is a low risk study. There are no risks involved in submitting sputum or urine for the study. You may feel some discomfort during swabbing of the back of the nose and during blood collection for HIV and viral load tests. Azithromycin and amoxicillin are already widely used in Malawi and rarely cause problems. Rare side effects for azithromycin include feeling nervousness, skin reactions and disturbance of heart function. Rare side-effects for amoxicillin are mental state changes, feeling light-headed, and reactions to sunlight.

The London School of Hygiene and Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation.

Will there be any benefits in this study?

The key benefit of this study is that you will have access to a more detailed TB evaluation process than usual. This will help you know if you have TB and to have the opportunity to start TB treatment. The study is also beneficial to health care providers because it will address important questions about use of antibiotics during the TB diagnostic process.

Will the findings in the study be confidential?

Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you. Information about TB test result and HIV test results will be recorded using an identification number. However, any records or data obtained as a result of your participation in this study may be used by LSHTM who are sponsoring this study, regulators of health research (COMREC), or by members of the research team. These records will be kept in a locked space in the University of Malawi College of Medicine. Information and samples collected in this study will be retained for up to 10 years after the end of the trial, according to our institution recommendations. These collected samples and other information may also be used for future studies if you give us that consent.

Can I withdraw from the study anytime and will this affect my treatment?

You are free to choose whether or not to participate in this study. While we would like you to participate in the study to the very end, withdrawing at any point is an option that is freely available to you without any penalty or loss of any entitled benefits. You will be provided with any significant new findings developed during the course of this study that may relate to or influence your willingness to continue participation.

What are the financial benefits of participating in this study?

There will be no payment given to you for participating in the study. The study will provide at least MK8,000 as compensation for your costs of attending the study visits. We will give this money in instalments on scheduled study visits.

Is this study approved by an ethics committee?

The study has been approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, and the College of Medicine Research Ethics Committee (COMREC).

Who do you ask if you have questions regarding the study?

If you have any questions concerning participation in this study, please feel free to ask me. Alternatively, you can contact the following people by phone or post:

	Name	Telephone	Postal address
Study investigators	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi
	Dr Marriott Nliwasa	0888681948	
COMREC			
	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

What is the benefit and unintended consequences of using antibiotics treatments as a way of excluding tuberculosis disease in patients with cough?

Patient declaration

Statement	Initial or thumbprint each box
I confirm that I have read the above information sheet for the above named study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. OR I have had the information explained to by study personnel in a language that I understand. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from LSHTM, University of Malawi College of Medicine, and COMREC, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that data about me may be shared via a public data repository or by sharing directly with other researchers, and that I will not be identifiable from this information	
I understand that the tissue sample collected from me will be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects	
I agree to take part in the above named study	

Printed name of participant	**Signature/thumb print of participant**	**Date**
Printed name of impartial witness*	**Signature of impartial witness***	**Date**

I attest that I have explained the study information accurately to _____, and was understood to the best of my knowledge by, the participant and that he/she has freely given their consent to participate* in the presence of the above named impartial witness (where applicable).

Printed name of staff obtaining consent	**Signature of staff obtaining consent**	**Date**

*Impartial witness should be someone the participant trusts. The impartial witness can write the participant name but cannot sign for them. Instead, illiterate participants should use thumbprint in place of signature and the impartial witness should go ahead and sign in designated space.

A copy of this informed consent document to be offered to the participant

Study title: Randomised controlled clinical trial of diagnostic value, clinical benefits and unintended consequences of using trial-of-antibiotics to evaluate ambulatory adults with prolonged cough for tuberculosis in Malawi

Version & Date: 3.0/28 Feb2019

Principal Investigator: Dr Titus H Divala REC ref: LSHTM 15232; COMREC P.04/18/2381

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PARTICIPANT INFORMATION SHEET

Chikalata chofotokozera ofuna kutenga nawo mbali

Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufifuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

Chiyambi

Tikukukupemphani kuti mutenge nawo mbali mu kafukufuku. Ndi chifuniro chanu kulowa mu kafukufukuyu. Musanapange chiganizo, mukuyenera kumvetsa chifukwa chimene kafukufukuyu akuchitikira komanso zimene zitadzachitike. M'modzi mwa anthu a gulu logwira ntchito mu kafukufuku awerenga chikalatachi pamodzi ndi inu, ndipo ayankha mafunso ena aliwonse amene mungakhale nawo. Funsani mafunso ngati simukumvetsa zomwe mwawerenga kapena ngati mukufuna uthenga owonjezera. Muli omasuka kulankhula ndi ena zokhudza kafukufukuyu ngati mukufuna. Ganizani mofatsa musanavomereze kutenga nawo mbali kapena ayi.

Kodi cholinga cha kafukufukuyu ndi chiyani?

Chifuwa chachikulu (TB) ndi matenda amene munthu amkhala chidwalire kwa nthawi yaitali. Odwalayo, amapanga makhololo. Ngakhale chili chochizika, chifuwa chachikulu ndi chovuta kuchipeza. Pamene njira zoyeza makholoro zalephera kupeza chifuwa chachikulu, achipatala amapereka mankhwala opha tizirombo toyambitsa matenda amene angathane ndi zonse zimene zimayambitsa zizindikiro za matenda ofanana ndi chifuwa chachikulu. Ngati odwala apeza bwino ndi njira imeneyi amaganiziridwa kuti alibe matenda a chifuwa chachikulu koma ngati sanapeze bwino amaganiziridwa kuti ali ndi chifuwa chachikulu. Cholinga cha kafukufuku ameneyu ndi kufuna kumvetsa za m'mene mankhwala amenewa amathandizira kusiyanitsa odwala matenda a chifuwa chachikulu ndi amene alibe matendawa, ngati mankhwalawa ali ndi phindu lina kwa odwala, komanso ngati kupereka mankhwalawa kukubweretsa tizirombo tosamva makhwala.

Tiphunzira zimenezi pakusiyanitsa gulu la anthu odwala amene apatsidwa mankhwala opha tizirombo toyambitsa matenda patsiku loyamba la kafukufukuyu ndi gulu lina limene silinapatsidwe mankhwalawa. Pakhala magulu awiri olandira mankhwala opha tizirombo motere: 1) Azitrhomycin omwedwa pilisi imodzi kamodzi patsiku kwa masiku atatu, komanso 2) Amoxicillin makapusolo anayi omwedwa katatu patsiku kwa masiku asanu. Gulu limene mulowe, mwa magulu atatuwa, lisankhidwa mwa mayere choncho mukhoza kupezeka mu gulu lina lirilonse.

Kodi chidzachitike ndi chiyani ngati ndingavomereze kutenga nawo mbali mu kafukufukuyu?

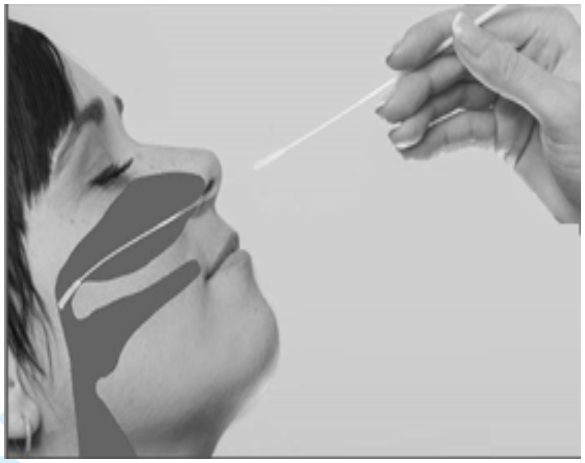
Tikukupemphani kuti mutenge nawo mbali mu kafukufukuyu chifukwa mwatiuza kuti muli ndi chifuwa. Odwala wina aliyense amene wakhala akukhosomola kwa masabata osachepera awiri, ali ndi zaka zosachepera 18, ndipo amakhala mu Blantyre muno, atha kutenga nawo mbali mu kafukufukuyu ngati alibe zizindikiro zosonyeza kudwalika kwambiri. Kupatula inu, tilemba anthu ena okwanira 1,874.

Zochitika za kafukufukuyu zidzapangidwa patsiku loyamba, pa sabata imodzi (Tsiku 8), ndi pamwezi umodzi (Tsiku 29). Pa masiku a kafukufuku onsewa, tidzakufunsani mafunso okhudzana ndi m'mene tingalumikizirane nanu, thanzi lanu, kagwiritsidwe ntchito ka mankhwala, ndi matenda ena aliwonse kapena kugonekedwa mu chipatala komwe kungakuchitikireni. Tidzalembanso zinthu zofunikira

kuchokera mu bukhu lanu la kuchipatala komanso zolembedwa zina za chipatala zimene mungakhale nazo.

Patsiku loyamba ndi pakutha pasabata yoyamba, tidzakufunsani kuti mupereke makhololo komanso mkodzo pofuna kuyeza matenda a chifuwa chachikulu. Ngati simungakwanitse kupereka makhololo patsiku loyamba, tidzakupatsani mabotolo kuti mudzawabweretse m'mawa wa tsiku lotsatira. Zotsatira zina za makhololo zidzatuluka pakutha pa masiku asanu ndi awiri ndipo tidzazipereka kwa matodolo a chipatala chino kuti akuthandizeni, zotsatira zina zidzatenga pafupi-fupi masabata anayi choncho mudzazilandira pa ulendo wa pamwezi umodzi. Zotsatira zanu zoyesa mikodzo ku matenda a chifuwa chachikulu sizidzakhalapo ku nkhani ya chisamaliro chanu cha kuchipatala.

Tidzayezanso kachirombo ka HIV. Ngati zotsatirazi zasonyeza kuti muli ndi kachirombo ka HIV tidzayeza kuchuluka kwa tizirombo ta HIV, komanso kukutumizani kolandilira chithandizo chamatendawa. Ngati tingakupezeni kuti muli ndi matenda a chifuwa chachikulu kapena kachirombo ka HIV panthawi ina iliyonse mkati mwa kafukufukuyu, tidzakutumizani kolandilira zithandizo zamatendawa pompano pachipatala.



Patsiku loyamba komanso pa ulendo wa mwezi woyamba, tidzapukuta kumbuyo kwa mkati mwa mphuno mwanu ngati m'mene zikuonekera pachithunzichi kuti titenge tizirombo timene timakhala m'menemo. Tidzayeza tizirombo timeneti kuti tione ngati tikumva mankhwala. Zotsatira zimenezi sizidzagwiritsidwa ntchito kuchisamaliro chanu chaku chipatala.

Pa ulendo wa sabata yoyamba, tidzakupemphani kuti mutiuze m'mene thanzi lanu lasinthira kuyerekeza ndi m'mene munaliri patsiku loyamba. Mafunso amenewa adzawerengedwa kwa inu kudzera pa makina a kompyuta ndipo mudzawayankha pakusankha mayankho angapo amene makinawa adzawonetse panthawi yomwe azidzafunsa.

Ulendo wa pa mwezi umodzi udzakhala wotsiriza umene tidzakupatseninso zotsatira za zoyesa za matenda a chifuwa chachikulu komanso tidzakufunsani ngati muli ndi zizindikiro za matenda a chifuwa chachikulu. Ngati panthawiyi mudzakhale kuti mukulandira Thandizo la HIV kapena TB, tidzakufuna kudziwa kuti zikuyenda bwanji. Kukumana ndi inu patatha mwezi umodzi ndikofunikira kwambiri chifukwa zidzakuthandizirani kuti mudziwe zotsatira za zoyeza za matenda a chifuwa chachikulu ndipo zidzatithandiziranso kudziwa zam'mene thanzi lanu liliri.

Maulendo a kuchipatala amene mudzayende a kafukufukuyu ndiwosachepera atatu. Pamenepa tikuwerenga tsiku loyamba, ulendo umodzi pakutha pa sabata imodzi, ndi ulendo umodzi pa mwezi umodzi. Ngati simunakwanitse kubwera kuno pa ulendo wina uliwonse tidzakukumbutsani pokuyimbirani lamya kapena tidzagwiritsa ntchito chilorezo ndi uthenga umene mudzatipatse kuti tikuyendereni kunyumba kwanu. Patsiku loyamba tidzakhala nanu kwa mphindi makumi asanu ndi imodzi, pamene paasiku ena onse, tidzakhala nanu kwa mphindi makumi atatu.

Kodi padzakhala ziopsezo zina zilizonse zochitika mu kafukufukuyu?

Kupanga nawo kafukufukuyu sikuika moyo wanu pa chiopsyezo chochuluka. Palibe chiopsezo pa kupereka makhololo kapena mikozo mu kafukufukuyu. Mukhoza kusamva bwino panthawi yopukuta kumbuyo kwa mphuno komanso panthawi yotenga magazi oyeza za kachirombo ka HIV ndi kuchuluka kwa tizirombo toyambitsa matendawa. Azithromycin ndi amoxicillin ndi mankhwala oti akhala akugwiritsidwa ntchito kwa nthawi yayitali m'Malawi ndipo sikweni-kweni kuyambitsa mavuto. Patali-patali azithromycin amapangitsa kumva nthumazi, ziwengo, komanso kusokonekera kwa kagwiridwe ntchito ka mtima. Patali-patali amoxicillin amapangitsa kusakhazikika mmanganizo, kumva chizungulire, komanso kutuluka ziwengo munthu akakhala padzuwa.

A London School of Hygiene ndi Tropical Medicine ali ndi thumba landalama zachipukuta misozi lokhudzana ndi kafukufukuyu. Ngati mwapweteka kapena kuvulala chifukwa chotenga nawo mbali mu kafukufukuyu, mudzakhale omasuka kupempha chipukuta misonzi.

Kodi padzakhala zopindula zina zilizonse mu kafukufukuyu?

Chopindulitsa chodziwika cha kafukufukuyu ndi chakuti mudzakhala ndi mwayi oyezedwa matenda a chifuwa chachikulu mozama kuposa m'mene zimakhalira nthawi zonse. Zimenezi zidzakuthandizirani kudziwa ngati muli ndi matenda a chifuwa chachikulu komanso kukhala ndi mwayi oyamba kulandira thandizo la mankhwala a chifuwa chachikulu. Kafukufukuyu ndi opindindulitsanso kwa opereka chisamaliro cha kuchipatala chifukwa adzayankha mafunso ofunikira okhudzana ndi kagwiritsidwe ntchito ka mankhwala opha tizirombo toyambitsa matenda panthawi ya ndondomeko yoyeza matenda a chifuwa chachikulu.

Kodi zotsatira za mukafukufukuyu zidzakhala za chinsinsi?

Chizindikiritso chanu mu kafukufukuyu chidzatengedwa kukhala cha chinsinsi. Zotsatira za kafukufukuyu, zikhoza kudzasindikizidwa ndi cholinga cha sayansi koma dzina lanu kapena chizindikiritso chilichonse chokhudzana ndi inu chidzabisidwa. Uthenga okhudza zotsatira zoyesa matenda achifuwa chachikulu kapena HIV zidzalembedwa pogwiritsa ntchito nambala yanu yakafukufuku. Komabe, zina zomwe mungatifotokozere zitha kudzagwiritsidwa ntchito ndi amene ali oyang'anira za kafukufuku wa zaumoyo (COMREC) komanso LSHTM. kapena ndi mamembala a gulu la kafukufukuyu. Zolembedwazi zidzasungidwa mumalo otsekedwa bwino ku sukulu ya ukachenjede ya Malawi College of Medicine. Uthenga ndi zoyesa zotengedwa mu kafukufukuyu zidzassungidwa kwa zaka pafupi-fupi khumi (10) pakutha pakuyesaku, malingana ndi ndondomeko ya bungwe lathu. Zoyesa zotengedwazi ndi mauthenga ena zikhoza kugwiritsidwanso ntchito pa kafukufuku wamtsogolo ngati mutatipatsa chilolezo chimenecho.

Kodi ndikhoza kusiya kafukufukuyu nthawi ina iliyonse ndipo zimenezi zingadzakhudze thandizo langa la mankhwala?

Muli ndi ufulu kusankha kutenga nawo mbali kapena kusatenga nawo mbali mu kafukufukuyu. Ngakhale tingakonde kuti mutenge nawo mbali mu kafukufukuyu mpaka ku mapeto, kutuluka nthawi iliyonse mukafukufuku ndi chisankho chanu popanda chilango chilli chonse kapena kuluza kulandira thandizo lililonse lomwe mukuyenera kulandira. Munthawi yakafukufukuyu, tidzakudziwitsani patati

patuluka mauthenga ena a sayansi ofotokoza zinthu zimene zingakupangitseni kuti mulingalirenso zachisamkho chanu chotenga nawo mbali.

Kodi pali phindu la ndalama lotani pakutenga nawo mbali mu kafukufukuyu?

Sipadzakhala kupatsidwa malipiro chifukwa chotenga nawo mbali mukafukufukuyu. Ndalama yomwe tidzakupatseni ndi yokwana MK8,000. Ndalamayi tizikupatsani pangonopango pamasiku anu akafukufuku..

Kodi kafukufukuyu ndiwovomerezeka ndi komiti yowona za ufulu wa anthu mukafukufuku?

Kafukufukuyu wavomerezedwa ndi London School of Hygiene & Tropical Medicine Research Ethics Committee, ndi College of Medicine Research Ethics Committee (COMREC).

Kodi mungafunse ndani ngati muli ndi mafunso okhudzana ndi kafukufukuyu?

Ngati muli ndi mafunso ena aliwonse okhudza kutenga nawo mbali mukafukufukuyu, chonde khalani omasuka kundifunsa. Munjira ina, mukhoza kulumikizana ndi anthu otsatirawa pa lamya kapena polemba kalata kumakeyala awa:

	Name **Dzina**	**Telephone** **Lamya**	**Postal address** **Adilesi**
Study investigators Akulu-akulu akafukufuku	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine
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COMREC	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

Kodi pali phindu lotani komanso zotsatira zosayembekezereka zotani pogwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ngati njira yothana ndi matenda a chifuwa chachikulu mu anthu amene ali ndi chifuwa?

Chitsimikizo cha odwala

Lembani mubokosi liri kumanjali mawu oyamba adzina lanu kapena dindani ndi chala ngati mukuvomereza

Mfundo yachitsimikizo	
Ndikutsimikiza kuti ndawerenga chikalata cha uthenga wa kafukufuku amene watchulidwa m'mwambamu. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira. KAPENA Ndafotokozeredwa uthengawu ndi akafukufuku mu chilankhulo chimene ndikuchimvetsa. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira.	
Ndikumvetsa kuti kutenga nawo mbali kwanga ndikosakakamizidwa ndipo ndili ndi ufulu kusiya panthawi ina iliyonse popanda kupereka chifukwa china chilichonse, popanda kukhudza chisamaliro cha kuchipatala kapena ufulu wanga.	
Ndikumvetsa kuti magawo ofunikira a zolembedwa zanga za ku chipatala komanso mu kafukufukuyu kuwonedwa ndi anthu ovomerezeka aku LSHTM, University of Malawi College of Medicine komanso COMREC, pamene kuli kofunika kutenga nawo mbali mukafukufukuyu. Ndikupereka chilolezo kwa anthu amenewa kuti athe kuwona za zolembedwa zanga.	
Ndikumvetsa kuti zomwe atolere akafukufuku zokhudza ine zikhoza kugawilidwa kwa anthu ena opanga kakafukufuku, ndipo kuti sipadzakhala chizindikiro chilichonse chosonyeza kuti zinachokera kwa ine.	
Ndikumvetsa kuti zoyeza za mthupi mwanga zimene zidzatengedwe kwa ine zidzagwiritsidwa ntchito kuthandizira kafukufuku wina mtsogolo, ndipo zikhoza kudzagawidwa mwachinsinsi ndi akafukufuku ena, pa ntchito yawo yovomerezeka ndi malamulo aowona zakafukufuku.	
Ndikuvomereza kutenga nawo mbali mu kafukufuku amene watchulidwa pamwambayu.	

Dzina la wotenga nawo mbali **Sayini/chidindo cha chala cha wotenga mbali** **Tsiku**

Dzina la mboni yopanda mbali* **Sayini ya mboni yopanda mbali** **Tsiku**

Ndikutsimikiza kuti ndafotokoza za uthenga wa kafukufukuyu molondola kwa _____, ndipo ine zinamveka monga mwakudziwa kwanga ndi, wotenga nawo mbali komanso kuti apereka chilolezo chawo kuti atenge nawo mbali* pamaso pa mboni yopanda mbali imene yatchulidwa pamwambapa (ngati kuli koyenera).

Dzina la wotenga chilolezo **Sayini ya wotenga chilolezo** **Tsiku**

*Mboni yopanda mbali ikuyenekera kukhala yokhulupiridwa ndi munthu ofuna kutenga nawo mukafukufukuyo. Mboni ikhoza kulemba dzina la munthu ofuna kutenga nawo mukafukufukuyo koma siingasayine mmalo mwake. Munthu ofuna kutenga nawo mukafukufuku, ngati samatha kuwerenga ndi kulemba, asayine ndi chidindo cha chala chake ndipo mboni isayine dzina ndi sayini. pamalo ambone.

Mpatseni otenga nawo mbali chikalata chimodzi kuti chikhale chake

Dzina la kafukufuku: Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufufuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	30
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	26

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4, 8, 22
Objectives	#7	Specific objectives or hypotheses	5, 10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, 6

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care	15

		providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P30, appendix (protocol)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P30, appendix (protocol)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P30, appendix (protocol)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	30 appendix (consent)
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	30 appendix (consent)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	30 appendix (consent)
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	30, appendix (protocol)
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	30, appendix (protocol)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25, and 28 appendix (protocol)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25, and 28 appendix (protocol)

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	30 appendix (consent)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	30 appendix (consent/protocol)

Notes:

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BMJ Open

Accuracy and Consequences of using Trial-of-antibiotics for TB diagnosis (ACT-TB Study): protocol for a randomised controlled clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033999.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2020
Complete List of Authors:	Divala, Titus; London School of Hygiene and Tropical Medicine, TB Centre; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative Fielding, Katherine; London School of Hygiene & Tropical Medicine, TB Centre; University of the Witwatersrand, School of Public Health Sloan, Derek; University of Saint Andrews, School of Medicine French, Neil; University of Liverpool Faculty of Health and Life Sciences, Centre for Global Vaccine Research, Institute of Infection and Global Health Nliwasa, Marriott; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; London School of Hygiene and Tropical Medicine, TB Centre MacPherson, Peter ; Liverpool School of Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme Kandulu, Chikondi; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; Malawi Liverpool Wellcome Trust Clinical Research Programme Chiume, Lingstone ; Malawi Liverpool Wellcome Trust Clinical Research Programme; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative Chilanga, Sanderson ; University of Malawi College of Medicine, Helse Nord Tuberculosis Initiative; Malawi Liverpool Wellcome Trust Clinical Research Programme Ndaferankhande, Masiye; Malawi Liverpool Wellcome Trust Clinical Research Programme Corbett, Elizabeth ; London School of Hygiene and Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Diagnostics, Epidemiology, Evidence based practice, General practice / Family practice, HIV/AIDS
Keywords:	trial-of-antibiotics, Tuberculosis < INFECTIOUS DISEASES, TB, antimicrobial resistance, diagnostic performance, antibiotics

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TITLE

Accuracy and Consequences of using *Trial-of-antibiotics* for TB diagnosis (ACT-TB Study): protocol for a randomised controlled clinical trial

Authors

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KEY WORDS

trial-of-antibiotics, tuberculosis, TB, antimicrobial resistance, AMR, antibiotics, diagnostic performance, sensitivity, specificity, randomised controlled clinical trial, randomised, RCT

Protocol version 4.0, 27 Jan 2020

ABSTRACT:

Introduction

Over 40% of global tuberculosis case notifications are diagnosed clinically without mycobacteriological confirmation. Standard diagnostic algorithms include "trial-of-antibiotics" –empirical antibiotic treatment given to mycobacteriology-negative individuals to treat infectious causes of symptoms other than tuberculosis, as a "rule-out" diagnostic test for tuberculosis. Potentially 26.5 million such antibiotic courses/year are prescribed globally for the 5.3 million/year mycobacteriology-negative patients, making trial-of-antibiotics the most common tuberculosis diagnostic, and a global-scale risk for antimicrobial resistance (AMR). Our systematic review found no randomised controlled trial (RCT) to support use of trial-of-antibiotic. The RCT aims to determine the diagnostic and clinical value and AMR consequences of trial-of-antibiotics.

Methods and analysis

A three-arm, open-label, RCT randomising (1:1:1) Malawian adults (≥18years) seeking primary care for cough into: a) azithromycin 500mg once daily for 3 days, or b)amoxicillin 1g three times/day for 5 days, or c) standard-of-care (no immediate antibiotic). We will perform Mycobacteriology tests (microscopy, Xpert/MTB/RIF and Mycobacterium-Tuberculosis culture) at baseline. We will use Audio-Computer-Assisted-Self-Interview (ACASI) to assess clinical improvement at day eight. First primary outcome will be proportion of patients reporting day-eight improvement out of those with negative mycobacteriology (specificity). Second primary outcome will be day 29 incidence of a composite endpoint of either death or; hospitalisation or; missed tuberculosis diagnosis. To determine AMR impact we compare proportion of resistant nasopharyngeal *Streptococcus pneumoniaee* isolates on day 29. 400 mycobacteriology-negative participants/arm will be required to detect a ≥10% absolute

difference in diagnostic specificity with 80% power. We will estimate measures of effect by comparing outcomes in antibiotic arms (combined and individually) to standard-of-care.

Ethics and dissemination

The study has been reviewed and approved by Malawi College of Medicine Research and Ethics Committee, London School of Hygiene &Tropical Medicine (LSHTM) Research Ethics Committee, and Regional Committee for Health and Research Ethics –Norway, and Malawi Pharmacy, Medicines, and Poisons Board (Appendix 1). We will present abstracts at relevant conferences, and prepare a manuscript for publication in a peer-reviewed journal.

Registration

Clinicaltrials.gov, NCT03545373

Strengths and limitations

- To our knowledge this is the first randomised controlled trial to address benefits and consequences of using antibiotics as an exclusion diagnostic for tuberculosis, a widely used practice that results in millions of antibiotic prescriptions/year.
- We will also contribute evidence on AMR affecting common antimicrobials used for managing respiratory infections.
- The use of ACASI for assessing clinical response and adherence to antibiotic treatment which can be used in future studies.
- Acknowledged weaknesses include limited power to evaluate safety of deferred antibiotic treatment; conduct subgroup analysis by HIV status; and the possibility that participants randomised to the standard-of-care arm may find alternative access to antibiotics therefore misclassifying exposure/intervention status.

INTRODUCTION

The high case-fatality rate for tuberculosis, the leading global infectious cause of death in adults[1] with approximately 10 million cases and 1.6 million deaths in 2017,[2] in part reflects suboptimal diagnostics.[3-6] To complement this diagnostic gap, standard algorithms throughout the world include a “trial-of-antibiotics” (Figure 1). This is a course of broad-spectrum antibiotics, with negligible *Mycobacterium tuberculosis* activity, given to patients with symptoms such as cough in order to “rule-out” or “rule in” tuberculosis.[7-9] In clinical practice and most national guidelines (summarised in figure 1), patients who have negative sputum mycobacteriology and have responded to antibiotic treatment are considered tuberculosis-negative while those who remain symptomatic are deemed likely to have tuberculosis and undergo further evaluations potentially leading on to receiving tuberculosis treatment.[7-9]

We estimate that 26.5 million courses of antibiotics are prescribed in the diagnosis of the 5.3 million smear negative tuberculosis registrations recorded annually,[10] making antibiotics the most common diagnostic for tuberculosis.[11] Our 26.5 million estimate assumes that for every one smear-negative tuberculosis case detected, five antibiotics courses are used: the first two courses being given to patients are ultimately registered as smear-negative tuberculosis, while the other three courses represent patients whose symptoms resolved without starting anti-tuberculosis treatment.[4 12] This high frequency of prescription of important broad-spectrum antibiotics raises a global-scale risk for antimicrobial resistance (AMR) which like tuberculosis, is a major crisis, becoming in 2016 one of only four health topics ever to be discussed at the United Nations General Assembly.[13-16]

We performed a systematic literature review[17] which demonstrated that, despite being in global and national guidelines for decades, trial-of-antibiotics has a limited supporting evidence base but with the available evidence suggesting poor diagnostic performance.[18] None of the identified studies was an RCT and most of the observational studies were very small and not primarily designed to assess the benefits and consequences of trial-of-antibiotics. Pooled sensitivity and specificity of trial-of-antibiotics versus mycobacteriology tests were below internationally defined minimum performance profiles for tuberculosis diagnostics.[19]

We hypothesise that use of antibiotics in the course of evaluating patients for tuberculosis has both benefits and risks that need to be weighed carefully to optimise patient and public health outcomes. We will address evidence gaps related to a) accuracy, b) antimicrobial resistance, and c) impact on clinical outcomes of trial-of-antibiotics by conducting an RCT (ACT-TB Study) recruiting adult patients with cough presenting to health centres in Blantyre, Malawi. To our knowledge this is the first randomised controlled trial to rigorously address these questions.

METHODS AND ANALYSIS

Study design

This is a three-arm individually randomised (1:1:1), open-label controlled clinical trial (RCT) investigating accuracy and broader clinical, and antimicrobial resistance impact of using trial-of-antibiotics to rule-out tuberculosis among adults presenting with cough at primary care centres in Malawi (Figure 2). The trial is registered with Clinicaltrials.gov (NCT03545373) (Appendix 2). The full trial protocol is provided as Appendix 3.

Study setting

We will screen adults aged at least 18 years presenting to Limbe and Ndirande health centres in Blantyre, Malawi. Blantyre has an estimated tuberculosis prevalence of 1,014 per 100,000 (95% CI: 486 to 1,542), and an estimated adult HIV prevalence of 12.7% (95% CI: 11.9 to 13.6).[20]

Eligibility criteria

We will offer enrolment to patients who satisfy the following inclusion and exclusion criteria.

Inclusion Criteria

- Ambulatory clinic attendees presenting with cough
- Unwell for at least 14 days
- Aged at least 18 years
- Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period.

Exclusion Criteria

- Self-reported allergy to study medications

- WHO/Malawi National tuberculosis Program (NTP) danger signs: respiratory rate > 30/min, temperature >39^{o}C, Heart rate >120/minute, confused/agitated, respiratory distress, systolic blood pressure <90 mmHg, inability to walk unassisted
- Treated with antibiotics other than co-trimoxazole prophylaxis within the past 14 days
- Tuberculosis treatment or isoniazid preventive therapy within the last 6 months

Interventions

We will randomise participants, in a ratio of 1:1:1, to the following arms:

- **Arm 1** (Azithromycin): Azithromycin 500mg taken once daily for 3 days from enrolment day
- **Arm 2** (Amoxicillin): Amoxicillin 1g taken three times daily for 5 days from enrolment day.
- **Arm 3** (Standard of care): No study antibiotic prescription.

Rationale for interventions

Amoxicillin was chosen because it is the standard antibiotic used as first line treatment and for trial-of-antibiotics in Malawi. However, amoxicillin may not demonstrate the best performance for trial-of-antibiotics because of increasing resistance, and a narrow coverage for aetiology of community acquired pneumonia and “atypical” organisms. We chose azithromycin to represent the optimal biological specificity of an oral regimen due to more complete coverage of atypical organisms that cause community acquired pneumonia (e.g mycoplasma and chlamydia), and also the low resistance rates in Malawi where macrolides are rarely used. The dose for Azithromycin is as recommended in the British National Formulary (BNF) as treatment for community acquired pneumonia.[21] The dose for amoxicillin is the BNF recommendation for severe infections but it is the recommended first line established by the Department of Medicine at Queen Elizabeth Central Hospital (Blantyre, Malawi) based on local microbiology.

Timing of interventions

The standard of care in Malawi defined by National Tuberculosis Programme guidelines for primary care patients presenting with cough who are otherwise well (no danger signs) is to take two sputum specimens for smear microscopy or Xpert and ask patients to return for

results, typically 3 days - 1 week later (Figure 1). The Malawi tuberculosis diagnostic algorithm recommends use of broad-spectrum antibiotics as trial-of-antibiotics after negative sputum tests are provided to patients who remain symptomatic. Therefore, the ideal population for randomisation for this study are patients on who already have negative results for smear microscopy or Xpert. However, that may have ethical challenges considering the implications of withholding treatment (if randomised to reference arm) from a symptomatic patient who, according to guidelines, should be given antibiotics. The first visit therefore was the most ideal time for randomisation and is in line with recommendations for test interval in investigations evaluating diagnostic tests with respect to the time interval between the index test (trial-of-antibiotics) and the reference test (mycobacteriology sputum sample collection). The timing also conforms to common clinical practice of prescribing trial-of-antibiotics at the same time as sputum collection to reduce diagnostic delay. The design was discussed with the District Health Office and the national tuberculosis programme ahead of ethics submission.

Known drug reactions

Azithromycin and amoxicillin have a long registration history, have been widely used globally and are well tolerated. Rare side effects for azithromycin include nervousness, dermatologic reactions including Stevens–Johnson syndrome, anaphylaxis and prolonged QT interval. Rare side-effects for amoxicillin are mental state changes, light-headedness, photosensitivity and severe allergic reactions.

Concomitant medication and interaction with other therapies

We do not have any restrictions with respect to concomitant medications apart from those listed in the exclusion criteria. We expect some participants to be on HIV antiretroviral drugs and some to subsequently start tuberculosis therapy. Important interactions therefore would be those those between the product and HIV antiretroviral drugs. There is no moderate or

major interaction between either azithromycin or amoxicillin with the classes of HIV antiretroviral drugs currently used in Malawi.

Trial restrictions

We do not require participants to have any dietary restrictions. We will also accept co-administration with contraception. Azithromycin and amoxicillin are both considered safe in pregnancy, so we will include pregnant women should they be eligible.

Assessment of compliance

On Day-8, we will document self-reported compliance adherence of study products.

Withdraw of interventions

The investigator may also terminate a participant from study product if indicated by an adverse reaction. If a participant stops taking study product either voluntarily or by investigator decision, they will be encouraged to remain in follow up and their data will form part of intention to treat analyses.

Study outcomes

The clinical trial has two separately powered, and distinctly assessed primary outcomes, one for diagnostic evaluation (Primary outcome 1: Day 8) and the other for clinical impact (Primary outcome 2: Day 29) of the intervention. The following are descriptions of all study outcomes:

Primary outcome 1: Specificity of day 8 symptom change versus mycobacteriology

The first primary outcome is the proportion of patients without tuberculosis (by sputum tests) who report improvement of their baseline illness when asked 7 days after randomisation (Day 8 study visit). This outcome can be thought of as diagnostic specificity if you take sputum test results as a reference standard and *change in symptoms at Day 8* as the

investigational test (Figure 3). In this case the possible results of the investigational test are improvement and no improvemet (no change or worsened) in response to the question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?*

As with all self-rated outcomes, social desirability bias (tendency of participants to answer questions in a manner that will be viewed favourably by healthcare worker), and interviewer bias (interviewers' subconscious or conscious influencing subject response) may affect the outcome. To minimise these biases in evaluation of improvement of baseline symptoms the interview will be conducted using Audio Computer Assisted Self-Interview (ACASI), a platform that allows patients to report their health state in private and directly into a database via an audio questionnaire administered by a tablet. The lack of human-to-human interaction will minimize interviewer, ascertainment, and social desirability biases. Another concern with open-label design is placebo-effect favouring those randomised to antibiotics over the standard of care arm that is however not addressed in our design.

We developed, piloted, and optimised the ACASI questionnaire in the study target population and arrived at the question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?* Before proceeding to the self-interview, participants will be oriented using test questions until study staff are sure that they will be able to go through the interview on their own. We will term ACASI interview outcome as **ACASI-test-negative** if the participant reports improvement or **ACASI-test-positive** if the participant reports no change or worsening (Figure 3).

The mycobacteriology reference standard will be defined in participants with at least one valid sputum test result on days 1 and 8 as **sputum-test-positive** if there is at least one positive of smear microscopy, Xpert/MTB/RIF, or MTB culture; and as **sputum-test-negative** if none of the tests is positive. To minimise bias, the sputum tests will be performed by a high-quality research laboratory in the University of Malawi College of Medicine by staff with no access to participant treatment allocation information or symptom results.

The specificity of day 8 symptom change (the index test measured using ACASI) against mycobacteriology tests (reference test) is defined as: **proportion of sputum-test-negative who are ACASI-test-negative.**

Primary outcome 2: Clinical impact of trial-of-antibiotics

We will investigate the overall clinical impact of trial-of-antibiotics by comparing the day 29 risk of any of death, hospitalisation, and "missed tuberculosis" (untreated mycobacteriological or radiological tuberculosis). All these events can lead to mortality and are potential consequences of trial-of-antibiotics; therefore, grouping them as a composite endpoint appropriately represents the effect of the intervention because: 1) there are similarities in the importance of each of the components, 2) the components occur with similar frequencies in the patient population, and 3) the direction of effect is anticipated to be the same for all.[22]

The connection between trial-of-antibiotics and risk of hospitalisation and death assumes a protective effect of antibiotics. In patients presenting with chronic cough at primary care in high HIV prevalence settings, frequencies of mortality and hospitalization over a two months period are similar, ranging from 2 to 6%.[23]

We have included missed tuberculosis diagnosis in our composite clinical outcome because this too can lead to death. We are defining "missed tuberculosis" as participants who meet standard mycobacteriological and radiological tuberculosis definitions but are incorrectly classified as tuberculosis-negative and not yet on tuberculosis treatment by Day 29. Clinical, radiological, and microbiological evaluation for tuberculosis will be done at Day 8, Day 29, as well as day between these two for patients who report worsening symptoms.

Secondary outcome 1: impact of trial-of-antibiotics on antimicrobial resistance

We will use *Streptococcus pneumoniae* isolated from swabs of the nasopharynx as the indicator pathogen for AMR evaluation. An ecological niche for many bacterial species, the

upper respiratory tract also presents a convenient window for investigating antimicrobial resistance. *Streptococcus pneumoniae* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract, acquires resistance readily, and has well documented laboratory investigation procedures in place.[24]

We will define **AMR positive** as having nasopharyngeal isolates of *Streptococcus pneumoniae* that are resistant to any of the following commonly used antibiotics: ceftriaxone, amoxycillin, cefoxitin, azithromycin, and erythromycin as determined using disc diffusion technique; and **AMR negative** as either (1) not isolating any *Streptococcus pneumoniae* or (2) isolating any *Streptococcus pneumoniae* that is not resistant to any of the assessed antibiotics. For each arm, and at both baseline and day 29, we will report proportion of AMR positive participants. The study outcome will be the proportion of AMR positive participants at day 29.

Secondary outcome 2: diagnostic value of trial-of-antibiotics in all patients including those without a valid sputum result

In this analysis, all will remain as described for primary outcome 1 except for the denominator, which will now include those without a valid sputum test result. The mycobacteriology reference standard for secondary outcome 2 will be defined as sputum test positive if at least one positive of smear microscopy, Xpert/MTB/RIF, or MTB culture from samples collected on days 1 and 8. The reference test will be sputum-test-negative if none of the tests is positive and where there is no valid sputum test result available. The most likely reason for not having a valid sputum result will be inability to produce sputum, but other explanations will be: lost sample before laboratory analysis, an invalid laboratory reading, or contamination. We have opted to analyse this population because in symptomatic adults of the study setting, failure to produce sputum can be as high as 13%.[23]

Secondary outcome 3: Economic evaluation

The objective of the economic evaluation is to undertake a cost-utility analysis to estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other. We will systematically compare costs and consequences associated with the interventions. We will perform a within trial comparison of the three treatment arms to estimate the incremental cost per quality-adjusted life year (QALY) gained for the azithromycin or amoxicillin arm in comparison to standard of care. Costs will be estimated from the Malawian Ministry of Health perspective. Health outcomes will be quantified in QALYs, estimated from participants' responses to the Chichewa version of the EQ-5D-3L, a Health quality of life (HRQoL) measure.[25 26] We will adopt a time horizon matching the length of participant follow-up to achieve the within trial evaluation.

Exploratory outcomes

Our exploratory analyses will be comparisons between the **azithromycin** and **amoxicillin** arms for all our primary and secondary outcomes.

Planned subgroup analyses

We will perform analysis of primary outcomes stratified by HIV status and by ART status as documented on enrolment day. This is important because the study site has high prevalence of HIV and associated bacterial infections which may be amenable to antibiotics used for trial-of-antibiotics.

Study procedures

Figure 2 and Table 1 presents the study time schedule including a summary of patient identification, baseline procedures and outcome ascertainment at day 8 and day 29 follow up visits.

Screening

Study staff will approach patients with symptoms of pulmonary tuberculosis (including cough of any duration, fever, weight loss, and night sweats) with information about the study and seek written informed consent (Appendix 4) from all patients who meet eligibility criteria. After consenting, a participant will be given a unique study identification number confirming enrolment.

Randomisation

Randomisation will be in the ratio 1:1:1 to the three arms of the trial, using block-randomisation with variable block sizes, and stratified by study site. An independent statistician will prepare the randomisation list using Ralloc command in Stata software, then print each allocation alongside a randomisation number, and seal in opaque envelopes. Upon confirming eligibility and consenting status a designated site staff will open the next available of sequentially numbered randomisation envelopes and administer the allocated study arm.

Blinding

The study is not placebo controlled because of funding limitations, and so will not use blinding due to the nature of the study design. However, study team masking will be maintained with all study outcome assessment occurring without reference to randomisation arm.

Baseline procedures

At baseline, we will collect demographic data, clinical history, record vital signs, height and weight. Participants will be requested to provide two sputum samples for Xpert/MTB/RIF and two more sputum samples the following morning for smear microscopy and MTB culture. We will also collect a urine sample for lipoarabamannan antigen detection (TB LAM); and a nasopharyngeal swab for pneumococcal culture and sensitivity testing. We will offer and perform HIV testing according to the national algorithm, and link all who test positive to care.

To minimise loss to follow up, we will collect contact phone numbers, a physical address and geolocation information.

Participant follow up

On day 8, the first activity (ahead of any other interaction with study staff) will be the ACASI. Other activities include providing results for day 1 tuberculosis tests and linking those who test positive to care; collection of another sputum sample for smear microscopy and *Mycobacterium tuberculosis* (MTB) culture; and management of ongoing symptoms and other illnesses. On visit day 29, the final study visit, we will document participant vital status, hospitalisations, and establish adherence to HIV and tuberculosis treatment. We will also collect nasopharyngeal swab samples from all participants, and sputum from those with tuberculosis symptoms.

Participant retention

To minimise loss to follow up, we will record geolocation information of participants' place of residence using ePAL android app, a high-resolution mapping system validated in Blantyre. We will also record up to 3 contact phone numbers of the participant and their nominated friends and relatives. We will not replace participants who discontinue study participation or study treatment regardless of reason for withdrawal or discontinuation or the time either of these occurs.

Data management

We will collect data using TeleForm (paper based system that uses optical character recognition) and Open Data Kit systems (ODK, an electronic data capture system installed on android devices). Data will be committed to a secure database located at Malawi-Liverpool Wellcome Trust (MLW) within 2 days for TeleForm, and 7 days for ODK.

373 **Table 1:** key study procedures over the study period

	STUDY PERIOD			
	Enrolment	Follow up		
TIMEPOINT	Day-1	Day-8		Day-29
ENROLMENT:				
Eligibility screen	x			
Informed consent	x			
Allocation	x			
INTERVENTIONS:				
Azithromycin	x			
Amoxicillin	x			
Standard of care	x			
ASSESSMENTS:				
Demographics	x			
History of antibiotic use	x	x		x
History & examination[1]	x	x		x
Sputum collection[2]	x	x		
Urine for TB LAM test[3]	x	x		
Nasopharyngeal swab for AMR[4]	x			x
HIV test	x			
Linking to routine care	x	x		x
ACASI[5]		x		
Clinical events[6]				x
Update contact & address		x		x

1. For symptomatic participants, Day-8 sputum mycobacteriology should be fast-tracked to inform care before they leave the clinic.
2. Give sputum bottles at end of Day-1 visit for submission on Day-8. Also collect sputum and perform mycobacteriology at any time of the study when clinically indicated
3. Urine Lipoarabinomannan for Tuberculosis Diagnosis (TB LAM)
4. Nasopharyngeal swab for Streptococcus pneumoniaeee culture and sensitivity as a way of determining risk of antimicrobial resistance (AMR)
5. Audio Computer Assisted Self-Interview (ACASI) for documenting change of symptoms on Day- 8 versus Day-1
6. Illnesses, clinic visits, radiological outcomes, new HIV diagnosis, new tuberculosis diagnosis, death, hospitalisation, missed tuberculosis diagnosis, HIV care loss to follow up, and tuberculosis care loss to follow up

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Statistical approach

We will summarise the processes of recruitment including non-eligibility and reasons of exclusion in a CONSORT (Consolidated Standards of Reporting Trials) flow chart. We will describe the study participants by their baseline characteristics, by arm. We will perform analyses of all our outcomes based on an intention to treat analysis (using the arm patient was randomised to). Analysis for primary outcome 1 will be restricted to participants with a valid sputum test result. We will report measures of effect from the following comparisons:

i) Azithromycin or amoxicillin (combined) versus standard of care
ii) azithromycin versus standard of care
iii) amoxicillin versus standard of care

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for study site. For each comparison, we will report 95% confidence intervals (CIs) and p-values from the likelihood test. If outcomes are rare, or the GLM model does not converge, we will use logistic regression to estimate the treatment effect using an odds ratio. We will not perform adjustments for multiple comparisons but will report all effect sizes with their 95% CIs and p-values to facilitate appropriate interpretation of our results.

We will perform data cleaning and analysis using Stata release 15 (Stata Corp, College station, Texas, USA). The statistical approach will be expanded in a detailed statistical analysis plan, which will be finalised before unblinding the study data.

Sample size and power

We performed power and sample size estimations for the diagnostic impact, clinical impact, and AMR impact outcomes as described below. Our sample size estimations are based on planned analysis that will use Chi-squared test for comparing two independent proportions.

Diagnostic impact outcome

We assume that at Day 8, change in well-being from baseline state in trial-of-antibiotics (azithromycin or amoxicillin) arms will correctly classify 60% of all mycobacteriology negative participants (i.e 60%specificity of day 8 symptom change in trial-of-antibiotics arms).[12] We wanted to estimate a sample size that would provide a discriminatory power of 80% at a two-sided significance level of 5%, to detect at least 10% difference in specificity (i.e ≤50% specificity of day 8 symptom change in standard of care arm).

Sample size for a combination of 2 antibiotic arms against standard of care arm

The sample size estimates along with assumptions for this comparison are shown in the Table 2A. To achieve the desired 80% discriminatory power, we will need to recruit at least 290 sputum-test-negative participants per arm. Accounting for TB prevalence, ability to produce and submit sputum, and loss-to-follow up increases the sample to 453 per arm or 1,359 for the whole study.

Table 2A: Sample size estimation for the *diagnostic impact outcome* comparing a combination of two antibiotic arms to standard of care arm (2:1 comparison)

POWER (X2 difference between independent proportions**)**	**Effect size (**50% SoC vs 60% amoxycillin or azithromycin**)**	**Effective sample per arm (**Sputum negative participants needed**)**
0.80	0.10	290
0.85	0.10	332
0.90	0.10	388

Target power and respective sample size estimates based on knowledge of TB risk, ability to produce and submit sputum, and loss-to-follow up.

Stata code: `power twoproportions .5 .6, test(chi2) power(0.80) nratio(2)`

Sample size for one antibiotic arm against standard of care arm

The sample size estimates along with assumptions for this comparison are shown in the Table 2B. To achieve the desired 80% discriminatory power, we will need to recruit at least

388 sputum-test-negative participants per arm. Accounting for TB prevalence, ability to produce and submit sputum, and loss-to-follow up increases the sample to 606 per arm or 1,819 for the whole study (The ethics approved protocol uses an older calculation that yields 625 per arm, and 1875 for whole study).

Table 2B: Sample size estimation for the *diagnostic impact outcome* one antibiotic arm to standard of care arm (pairwise comparison)

POWER (X2 difference between independent proportions**)**	**Effect size (**50% SoC vs 60% amoxycillin or azithromycin**)**	**Effective sample per arm (**Sputum negative participants needed**)**
0.80	0.10	388
0.85	0.10	443
0.90	0.10	519

Target power and respective sample size estimates based on knowledge of TB risk, ability to produce and submit sputum, and loss-to-follow up.

Stata code: `power twoproportions .5 .6, test(chi2) power(0.80) nratio(1)`

Power for clinical impact outcome

For the clinical impact of trial-of-antibiotics outcome, we assume a 4% baseline risk of composite outcome, and a loss to follow up of 10% by Day 29. Using the sample size of 625 participants per arm (obtained in Table 2B), and a type I alpha of 5%, we will be able to detect the difference between arms with 80% power, if the risk in the intervention arm is twice that of the standard of care arm. This estimate is applicable to all comparisons shown in section 3.

Power for AMR outcome

Study arms will be compared based proportion of participants with resistant *Streptococcus pneumoniae* on day 29. We assume that 45% of Day-29 nasopharyngeal swabs will successfully grow *Streptococcus pneumoniae,* and that 10% of the isolates will meet the definition of resistance (described earlier under outcomes), and that 10% will be lost to follow up by Day 29. Therefore, on day 29, the standard of care arm (of 625 participants) will have

253 *Streptococcus pneumoniae* isolates, 25 of which would meet the definition of resistance. This translates into a 4% (25/625) risk of AMR positive cases in the standard of care arm. To detect a twofold change in odds of day 29 AMR risk with at least 80% power, using Pearson's Chi-squared test, at 0.05 alpha, we will need at least 431 and 553 participants per arm for the 2:1 and pairwise comparisons respectively.

Monitoring and oversight

The trial will be monitored by the Research Support Centre Clinical Trials Unit of the University of Malawi College of Medicine. An independent Data and Safety Monitoring Board (DSMB), and a Trial Steering Committee (TSC) have been set up and meet bi-annually.

Trial closure

We will consider the trial closed after completing follow up of the last enrolled participant, and upon recording all mycobacteriology laboratory reports. Antimicrobial resistance lab work will continue beyond trial closure. The trial may be terminated early by the trial steering committee upon recommendation of the DSMB. The halting rule for a trial arm is an unacceptable high level of deaths assessed using an alpha determined at the first DSMB meeting.

PATIENT AND PUBLIC INVOLVEMENT

Patients were involved in the design of the study especially the audio-computer-assisted interview (ACASI) used for collecting primary outcome data. Health workers were involved in the design of study visits and patient flow.

DISCUSSION

The ACT-TB study will investigate the benefits and consequences of “trial-of-antibiotics,” a widely promoted approach to many patients with suspected tuberculosis in low- and middle-

income countries without solid evidence base. To our knowledge, ACT-TB Study is the first RCT of this kind. Results of our trial will add to the evidence-base regarding routine diagnosis of tuberculosis in low and middle-income countries and strengthen our fight against AMR. Both tuberculosis and AMR are diseases of major importance globally, with tuberculosis causing an estimated 1.6 million deaths in 2017 and AMR projected to cause 10 million deaths per year by 2050.[2 27]

Choice of study interventions

We have chosen amoxicillin because it is the first line treatment for outpatient management of pneumonia in Malawi and is commonly used for trial-of-antibiotics. It also provides data of immediate programmatic relevance and a starting point to investigate exacerbation of pre-existing AMR pressure. However, amoxicillin may not demonstrate the full benefits for trial-of-antibiotics because of organisms with intrinsic ("atypicals") or acquired (common in gram-negative organisms, and *Staphylococcus aureus*) penicillin resistance.[28] Oral antibiotics that may provide the better diagnostic discrimination for bacterial versus mycobacterial causes of cough are macrolides, such as azithromycin, because of better intrinsic coverage of "atypical" intracellular organisms such as *mycoplasma* species that cause community acquired pneumonia,[29-31] and low levels of acquired macrolide-resistance in bacterial isolates in Malawi.[28]

ACASI for post-treatment improvement assessment

Our systematic review[18] did not identify a consistent definition of tuberculosis or no tuberculosis based on trial-of-antibiotics. A definition of clinical change following antibiotic treatment is necessary for the trial-of-antibiotics as this determines who get categorised as well or tuberculosis-positive. Approaches that ranged from self-reported improvement to a combination of clinical and radiological assessments are likely to be highly subjective and prone to bias, as well as being a potentially avoidable source of heterogeneity between

studies. In this study, we hope to address these biases (particularly, inter-observer variability, and patient/interviewer reporting or ascertainment biases) by using self-rated change of illness (on day 8) recorded using a self-completed questionnaire, the ACASI (described under outcomes). The ACASI questionnaire, the delivery platform, and the resulting data management can all be replicated in future studies, creating potential for more standardisation in assessment of clinical response to treatment.

Potential clinical impact of antibiotics

In areas with high HIV prevalence, empirical antibiotics during tuberculosis investigations could be life-saving: mortality immediately before and after tuberculosis diagnosis is high, [3 32] and is often secondary to severe bacterial infections.[32-34] The leading aetiologies of infection and death on tuberculosis treatment as well as among outpatients with tuberculosis-like symptoms are *Streptococcus pneumoniaee* and non-typhoidal salmonellae: both can present with cough (primary cause) or as co-morbidities (super-infections) in patients presenting with active *Mycobacterium tuberculosis* disease.[32-34] If effective treatment of this type of life-threatening primary/super-infections reduces mortality during the diagnostic work-up of suspected tuberculosis in people living with HIV, then empirical use of broad-spectrum antibiotics would be indicated for this purpose alone, irrespective of any diagnostic contribution to tuberculosis treatment decisions. In this context, azithromycin may be the most effective arm, as salmonella infections are highly sensitive to azithromycin, but not to amoxicillin.[28]

AMR and trial-of-antibiotics

Antimicrobial resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been investigated before. Previous work has shown that empirical antibiotics can drive rapid emergence of antimicrobial resistance.[35 36] Co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal

resistance in bloodstream infections by 2010[37]. Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniaee*, but with increased macrolide-resistance 6 months later.[38 39]

In this study we have the opportunity to assess the extent to which brief exposure drives antimicrobial resistance during diagnostic work-up for tuberculosis. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient sampling opportunity for investigating antimicrobial resistance.[40] *Streptococcus pneumoniae* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract, acquires resistance readily, and has well documented laboratory investigation procedures in place.[24] As exploratory analyses, we will also assess nasopharygeal colonization and antimicrobial resistance in relation to tuberculosis treatment and HIV status.

Important subgroups

Clinical response to trial-of-antibiotics is possible and indeed well-described in patients with bacteriologically confirmed tuberculosis (i.e. false-negatives/low sensitivity from the perspective of tuberculosis diagnosis) may relate to multiple super-infections.[4 33] As such, this phenomenon may vary by HIV status, since multiple concurrent infections are a hallmark of advanced HIV immunosuppression, and are most commonly reported in patients with suspected tuberculosis in the pre-ART era. In 2015, in Malawi, 45% of adults who presented to primary care with prolonged cough (≥2 weeks) were HIV-positive, of whom only ~20% started tuberculosis treatment on the basis of positive mycobacteriology.[23] As such, the benefits and consequences of trial-of-antibiotics may vary by HIV status and ART coverage, and by subsequent tuberculosis treatment decisions. We will, therefore, include a pre-specified sub-analysis of trial outcomes stratified by HIV and ART status.

Limitations

The study has several limitations. Firstly, we did not use a placebo-control arm. Secondly, the study is not adequately powered to evaluate safety of deferred antibiotic treatment or conduct subgroup analyses of outcomes by HIV status, both which are important evidence gaps. Other limitations include the possibility that participants randomised to the standard-of-care arm may find alternative access to antibiotics therefore misclassifying exposure/intervention status. There is also a possibility of misclassifying active tuberculosis status because of the suboptimal nature of the available tests.

ETHICS AND DISSEMINATION

The study has been reviewed and approved by the University of Malawi College of Medicine Research and Ethics Committee (COMREC; registration number P.04/18/2381), the London School of Hygiene & Tropical Medicine Research Ethics Committee (LSHTM EC; registration number 15232), and Regional Committee for Health and Research Ethics, NTNU-Midt, Norway (REK nord; registration number 208/1964). Regulatory approval has been granted by the Malawi Pharmacy, Medicines, and Poisons Board (PMPB; registration number CTRC/III/14062018102). We will present any future protocol modifications to these bodies before implementing. We will submit results for publication in a peer-reviewed journal. We will submit abstracts to relevant national and international conferences. This work will also form part of a PhD thesis for TD, which he will submit to the LSHTM. This study will follow the standards set by CONSORT guidelines.

AUTHORS' CONTRIBUTIONS

THD, KF and ELC are the main contributors to the conception, and design of the study. DS, MN and PM contributed to the general study planning and clinical design. NF contributed to the general study planning and antimicrobial resistance design. CK, LC, SC, and MJN contributed to the design, piloting, and refining of study and clinical procedures. THD developed the first draft of the manuscript. All authors carefully reviewed and substantially

contributed to the development of the trial protocol and this manuscript. All authors read and approved the final manuscript. THD is the guarantor for this work.

FUNDING AND SPONSORSHIP STATEMENT

The clinical trial is funded by the Commonwealth Scholarship Commission and the Helse Nord RHF grant awarded to THD. This work is part of THD's PhD work at London School of Hygiene & Tropical Medicine (LSHTM). LSHTM is the sponsor of this clinical trial (sponsor address: Keppel Street, Bloomsbury, London WC1E 7HT). ELC is funded by a Wellcome Trust Senior Research Fellowship in Clinical Science: WT200901. The funding agencies and the sponsor had no role in the preparation of the protocol or the intention to submit this manuscript for publication.

COMPETING INTERESTS STATEMENT

We have no conflicts of interest to declare.

BODY WORD COUNT: 4,034

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Sensibilité aux macrolides des isolats bactériens provenant des infections acquises dans la communauté en Afrique subsaharienne et en Asie
Susceptibilidad a macrólidos de aislados bacterianos provenientes de infecciones adquiridas en la comunidad. *Tropical Medicine & International Health* 2011;16(10):1192-205. doi: 10.1111/j.1365-3156.2011.02837.x

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LEGENDS FOR FIGURES

1. Legend for figure 1

*The common clinical practice is that outpatients start antibiotics at the time of submitting sputum, to avoid the need for a third clinic visit to complete the algorithm.

Figure 1: The position of trial-of-antibiotics in standard algorithms for diagnosis of tuberculosis in low and middle income countries (based on the 2018 WHO GLI model guidelines and as implemented in national guidelines e.g Ghana, Malawi and South Africa.)

2. Legend for figure 2

ART = antiretroviral treatment for HIV

NTP = Malawi National Tuberculosis Program

TB LAM = Urine Lipoarabinomannan for Tuberculosis Diagnosis

VL = HIV Viral load

Figure 2: Flow diagram for the clinical trial in Blantyre, Malawi

3. Legend for figure 3

Figure 3: Assessing the diagnostic value of a change in symptoms from baseline to day 8

APPENDIX 1: ETHICS AND REGULATORY APPROVALS

(attached separately)

APPENDIX 2: TRIAL REGISTRATION—DATA SET

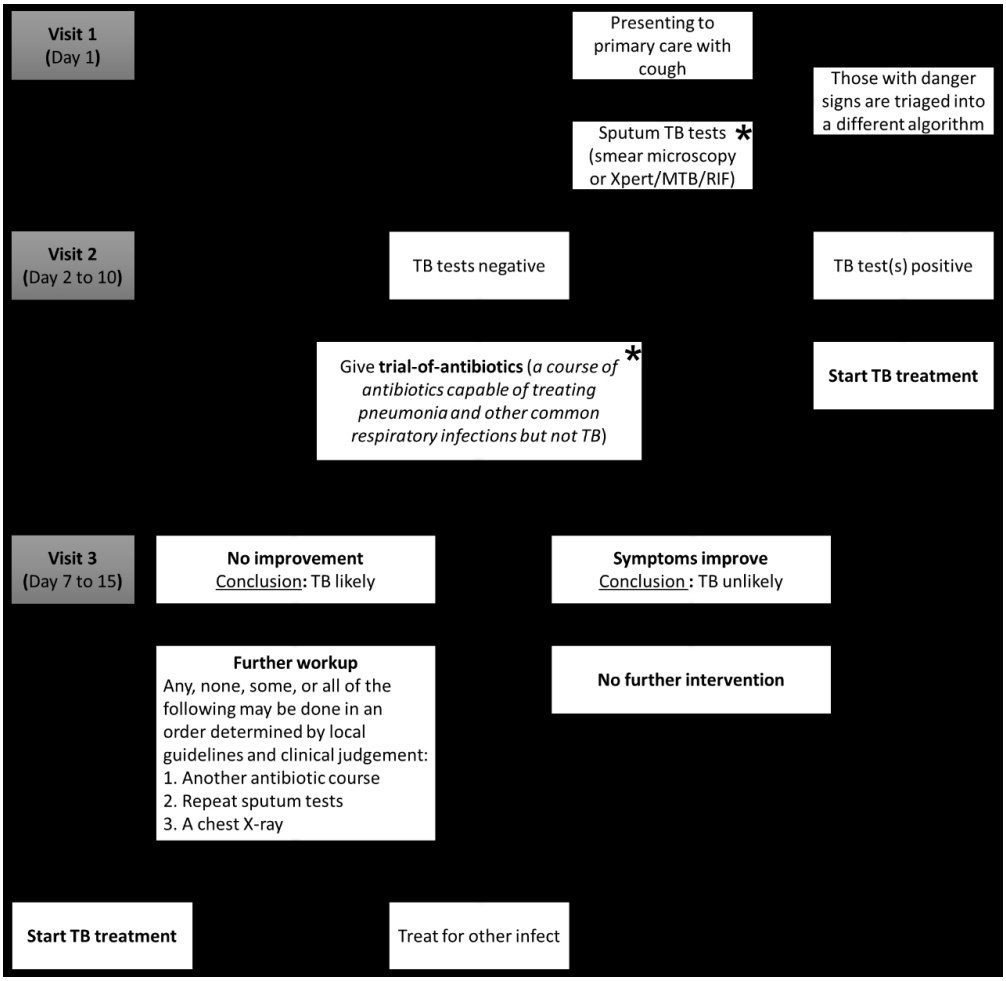
(attached separately)

APPENDIX 3: FULL TRIAL PROTOCOL

(attached separately)

APPENDIX 4:PATIENT INFORMATION SHEET AND INFORMED CONSENT

(attached separately)



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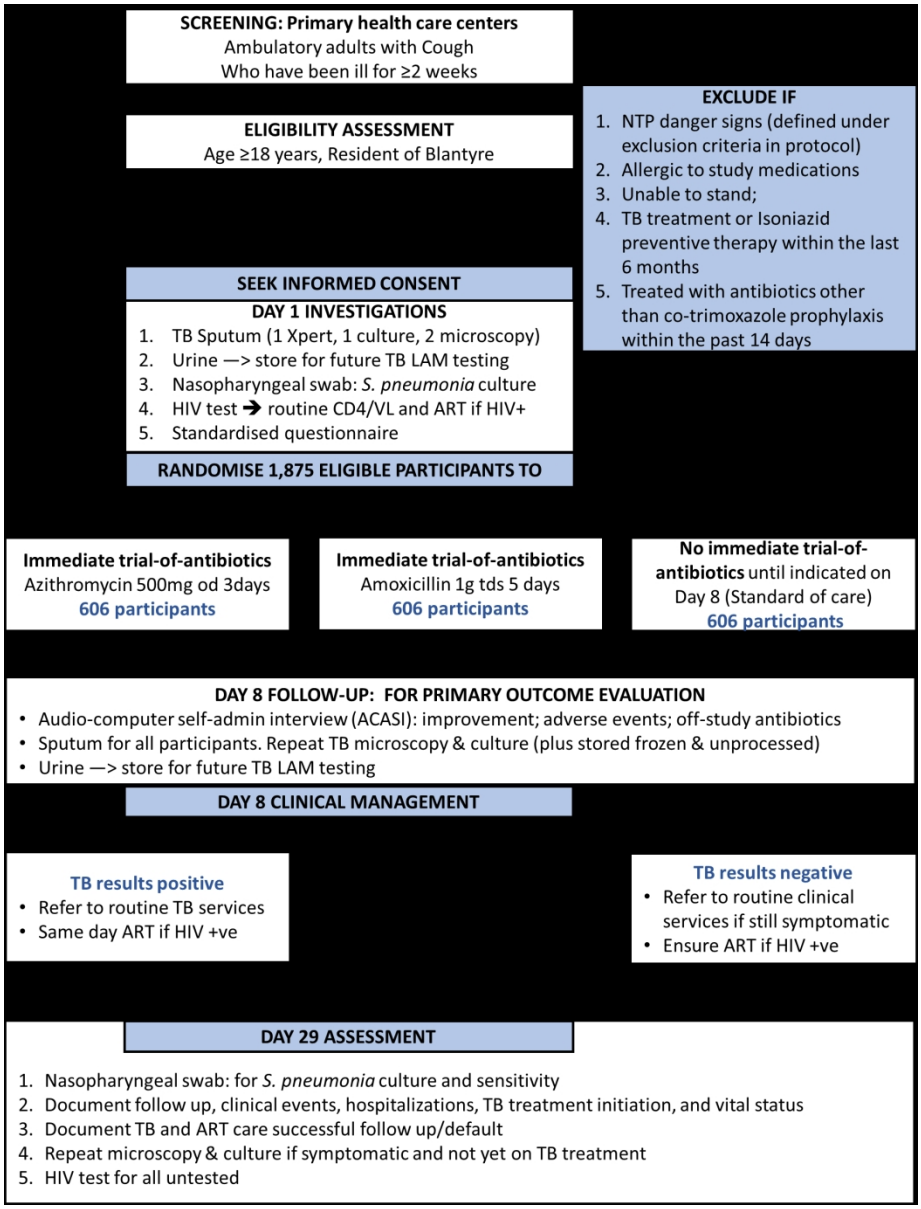

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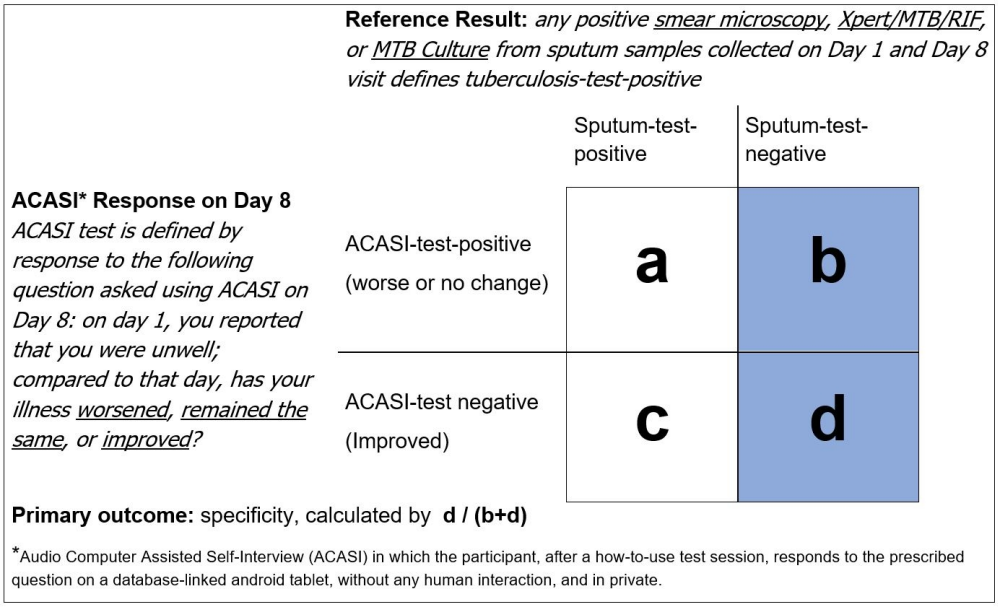

Figure 3: Assessing the diagnostic value of a change in symptoms from baseline to day 8

366x222mm (96 x 96 DPI)

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.04/18/2381 - Accurancy and Consequences of using Trial-of-antibiotics for TB diagnosis (ACT-TB Study) by Titus H Divala

On 03-Jul-18

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

Mlombe 03-Jul-18

Dr. YB. Mlombe - Chairperson (COMREC) Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an interim report in the course of the study and an end of study report.

4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 03-Jul-19. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

PHARMACY, MEDICINES & POISONS BOARD

Mission: To promote and improve the health of the population of Malawi through the regulation of Pharmacy Personnel, Pharmacy Businesses, Medicines and Allied Substances

ALL CORRESPONDENCE SHOULD BE ADDRESSED TO THE REGISTRAR

Head Office:
Off Paul Kagame/
Chilambula Road
P.O.Box 30241
Capital City
LILONGWE 3, MALAWI

Phone: (+265) 01 755 165
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Email: info@pmpb.mw
Web: www.pmpb.mw

PMPB/CTRC/III/14062018102
DATE: 4th July, 2018

Department of Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine
Keppel St
London

Attn.: Dr. Titus Divala

RE: ACCURACY AND CONSEQUENCES OF USING TRIAL-OF-ANTIBIOTICS FOR TB DIAGNOSIS (ACT-TB STUDY).

Refer to your application to register the above mentioned clinical trial with the Pharmacy, Medicines and Poisons Board (PMPB).

The Clinical Trial Review Committee (CTRC), at its meeting held on 22nd June, 2018, issued a **No Objection** to the implementation of the trial after members agreed that the nature of the trial was seen to be outside the scope of trials that should be regulated by PMPB through the CTRC.

Please contact the undersigned if there are any issues that need further clarification.

Yours faithfully,

M. Kawaye
ACTING REGISTRAR

PHARMACY MEDICINES & POISONS BOARD
REGISTRAR
04 JUL 2018
P.O. BOX 30241, LILONGWE 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			06.11.2018	2018/1964/REK nord
			Deres dato:	Deres referanse:
			25.09.2018	

Vår referanse må oppgis ved alle henvendelser

Jon Øyvind Odland
Institutt for samfunnsmedisin

2018/1964 En kontrollert klinisk studie for å undersøke responsen til bredspekret antibiotika som en eksklusjonsdiagnose i allmenpraksis mot risiko for antibiotika resistens

Forskningsansvarlig institusjon: UiT Norges arktiske universitet
Prosjektleder: Jon Øyvind Odland

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 25.10.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hforskn) § 10.

Prosjektleders prosjektomtale
Det skal undersøkes, ved hjelp av en randomisert, kontrollert studie om respons til bredspekret antibiotika kan brukes som eksklusjonsdiagnose for tuberkulose. Dette skal vurderes opp mot risiko for resistensutvikling knyttet til behandingen. Tre grupper (625 per gruppe) individuelt randomisert (1:1:1), med åpen informasjon undersøkes med standard diagnostisk tilnærming. Kun voksne deltakere, med full brukermedvirkning og informert samtykke. Studien kan forenkle dignostikk og klinikk for en utsatt gruppe mennesker. Studien skal i sin helhet foregå i Malawi. Alle etiske godkjenninger fra Malawi og London er vedlagt.

Komiteen vurderte at Hanne Husom Haukland var inhabil og hun fratrådte møtet da saken ble behandlet, jf. fvl. § 6.

Om prosjektet
Prosjektet er en del av en PhD. Studenten skal avlegge sin PhD i London.

Dette er et samarbeidsprosjekt mellom Universitetet i Malawi, London School of Hygiene and Tropical Medicine, og Universitetet i Tromsø.

Prosjektet skal gjennomføres i Malawi og er et «Tuberkulose initiativ» fra Helse Nord.

Det foreligger godkjenning fra London School of Hygiene and Tropical Medicine, og University of Malawi.

Data
Det skal hentes data fra pasientjournal og fra lokale poliklinikker. Data er standard medisinske opplysninger knyttet til infeksjoner og sykehistorie.

Nye helseopplysninger er respons på behandling av infeksjoner.

Data avidentifiseres med koblingsnøkkel. Database oppbevares i 5 år i Malawi.

Deltakere/rekruttering
Voksne deltakere fordeles i tre grupper voksne deltakere (625 per gruppe), individuelt randomisert. Deltakere rekrutteres gjennom behandling på poliklinikkene.

REK har ingen innvendinger til prosjektet

Vedtak
REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider og godkjenner det med hjemmel i helseforskningsloven § 10. REK forutsetter at prosjektet også har godkjenning fra Malawi.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 21.03.2022, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:jon.oyvind.odland@uit.no

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

9 May 2018

Dear Titus ,

Study Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

LSHTM ethics ref: 15232

Thank you for your application for the above research, which has now been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Safety Information	ACT_PackageInsertAzithromycin	14/03/2013	JUNE 2013
Safety Information	ACT_PackageInsertAmoxicillin	21/12/2015	DEC 2015
Sponsor Letter	2018-KEP-077_Sponsor Confirmation_13.03.18	13/03/2018	1
Other	GCP Cert_LSHTM_TDivala_21.03.18	21/03/2018	1
Investigator CV	ACT-CV1_TitusDivala	30/03/2018	1
Investigator CV	ACT-CV2_KatherineFielding	30/03/2018	1
Investigator CV	ACT-CV3_LizCorbett	30/03/2018	1
Information Sheet	ACT-20180330InformedConsentEnglish	30/03/2018	1.0
Information Sheet	ACT-20180330InformedConsentChichewa	30/03/2018	1.0
Protocol / Proposal	ACT-20180330Protocol	30/03/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Dr Titus Divala
LSHTM

12/04/2019

Dear Titus,

Project Title: RCT investigating if benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis in primary care adult patients outweigh the risk of antimicrobial resistance

Project ID: 15232

Thank you for your annual report application for the continuation of your research dated 09/04/2019 12:01 , which has now been considered by the Chair on behalf of the Ethics Committee.

Confirmation of ethical opinion

This application is approved by the committee for a further year.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

After ethical review

Any changes to the application must be submitted to the committee via an Amendment form.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reaction (SUSARs) which occur during the project by submitting a SUSAR and Protocol Violation form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

APPENDIX 2: TRIAL REGISTRATION—DATA SET

NCT Number	NCT03545373
Title	Accuracy and Consequences of Using Trial-of-antibiotics for TB Diagnosis (ACT-TB Study)
Acronym	ACT-TB
Status	Recruiting
Study Results	No Results Available
Conditions	Tuberculosis|Respiratory Tract Infections|Pneumonia
Interventions	Drug: Azithromycin|Drug: Amoxicillin
Outcome Measures	Diagnostic accuracy of trial-of-antibiotics: Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 against a mycobacteriology reference standard.|Overall clinical benefit of empirical antibiotic treatment in primary care participants with chronic cough: proportion of participants experiencing adverse clinical outcomes|Impact of trial-of-antibiotics on antimicrobial resistance|Diagnostic accuracy of trial-of-antibiotics including participants who did not produce sputum|Economic analysis of use of trial-of-antibiotics
Sponsor/Collaborators	London School of Hygiene and Tropical Medicine|University of Malawi College of Medicine
Gender	All
Age	18 Years and older Â (Adult, Older Adult)
Phases	Phase 3
Enrollment	1875
Funded Bys	Other
Study Type	Interventional
Study Designs	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Diagnostic
Other IDs	15232
Start Date	February 25, 2019
Primary Completion Date	Jun-20
Completion Date	Jun-20
First Posted	June 4, 2018
Results First Posted	
Last Update Posted	August 15, 2019
Locations	University of Malawi College of Medicine, Blantyre, Southern, Malawi
Study Documents	
URL	https://ClinicalTrials.gov/show/NCT03545373

Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis (TB) in primary care adult patients versus risk of antimicrobial resistance (AMR)

Short title:	**A**ccuracy and **C**onsequences of using **T**rial-of-antibiotics for **TB** diagnosis
Acronym:	ACT-TB Study
Trial registration:	
Protocol version:	4.0, 27 Jan 2020
Chief Investigator:	Titus H Divala London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT Tel: +44 740 523 1847 Email: titus.divala@lshtm.ac.uk
Co-Investigators:	Katherine L Fielding, Neil French, Derek J Sloan, Elizabeth L Corbett
Collaborators:	Marriott Nliwasa, Augustine Choko, Ankur Gupta-Wright, Jennifer Cornic, Jon Øyvind Odland, Chisomo Msefula, Hendramoorthy Maheswaran
Sponsor:	London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office: London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT Tel: +44 207 927 2626 Email: RGIO@lshtm.ac.uk
Funding:	Helse Nord RHF Tromsø, Norway; Tel: +47 97065144 Email: Hanne.Husom.Haukland@helse-nord.no
Study Coordination Centre:	University of Malawi College of Medicine Private Bag 360 Chichiri, Blantyre, Malawi Tel: +2651871911 Email: rscdirector@medcol.mw

This trial will adhere to the principles outlined in the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

Table of contents

1 Abbreviations

ACASI	Audio Computer Assisted Self-Interview
AE	Adverse Event
AMR	Antimicrobial Resistance
AR	Adverse Reaction
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CEACs	Cost-Effectiveness Acceptability Curves
COMREC	University of Malawi College of Medicine Research and Ethics Committee
CXR	Chest X-Ray
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety and Monitoring Board
GLM	Generalised Linear Model
HIV	Human Immunodeficiency Virus
HRQoL	Health Quality of Life
LAM	Urine Lipoarabinomannan Assay
LJ	Lowenstein-Jensen
LSHTM	London School of Hygiene & Tropical Medicine
MDA	Mass Drug Administration
MGIT	Mycobacteria Growth Indicator Tube

MTB or M.tb	*Mycobacterium tuberculosis*
NMBs	Net Monetary Benefits
NTM	Non-Tuberculous Mycobacteria
NTP	National Tuberculosis Control Program
NTS	Non-Typhoidal Salmonellae
PCP	Pneumocystis Jiroveci
PLHIV	People Living With HIV
PTB	Pulmonary Tuberculosis
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOC	Standard of Care
STGG	Skim Milk Tryptone Glucose Glycerol
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
WHO	World Health Organization
WTP	Willingness to Pay

2 Study Summary

Title	Randomised controlled clinical trial investigating benefits of using response to broad spectrum antibiotics as an exclusion diagnostic for tuberculosis (TB) in primary care adult patients versus risk of antimicrobial resistance (AMR)
Design	Three arm (625 per arm) individually randomised (1:1:1), open-label controlled clinical trial investigating standard care diagnostic approach for tuberculosis. The trial will not use any unlicensed products.

Objective	**Outcomes**
Primary	
1. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults with prolonged cough (and have a valid sputum test result) at primary care level in Malawi.	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among participants with a valid result from at least one sputum TB test
2. To determine the overall clinical benefit of giving empirical antibiotic treatment in primary care participants with chronic cough.	Proportion of participants experiencing at least one of the following adverse outcomes by Day 29: 1) death 2) hospitalisation 3) missed TB diagnosis
Secondary	
3. To evaluate using nasopharyngeal Streptococcus pneumonia, the effect of a trial-of-antibiotics on selection for antimicrobial resistance.	Proportion of Day 29 nasopharyngeal *Streptococcus pneumoniae* isolates resistant to commonly used antimicrobials.
4. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in primary care presenting Malawian adults with prolonged cough including those without a successful sputum	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among all

test (unable to submit sputum and those with invalid sputum results).	randomised participants, with those who could not provide sputum or had an invalid sputum result classified as mycobacteriologically negative.
5. To estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other.	• Incremental cost per quality adjusted life year gained • Total direct medical costs per participant over 56 days • Eq-5D utility score
Exploratory	
Our exploratory analyses will be comparisons between the azithromycin and amoxicillin arms for all our primary and secondary outcomes.	
Population	Adults presenting to primary care centres in Malawi reporting cough.
	Inclusion criteria: • Ambulatory clinic attendees presenting with cough • Should have been ill for ≥ 14 days • Aged at least 18 years • Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period. Exclusion criteria: • Self-reported allergy to study medications • Acute danger signs defined in national TB treatment guidelines • Tuberculosis treatment or isoniazid preventive therapy in the last 6 months • Treated with antibiotics, other than co-trimoxazole prophylaxis, for the current illness or within the past 14 days
Treatment	**Arm 1**: Azithromycin 500mg once daily for 3 days commencing on randomization day. **Arm 2**: Amoxicillin 1 g 3 times daily for 5 days commencing on randomization day. **Arm 3**: Standard of care in current national guidelines for patients presenting with cough and without danger signs (No treatment until re-evaluation with sputum TB test results)
Duration	We will give treatments on the randomisation day (Day-1) and perform follow up activities on days 8, and 29.

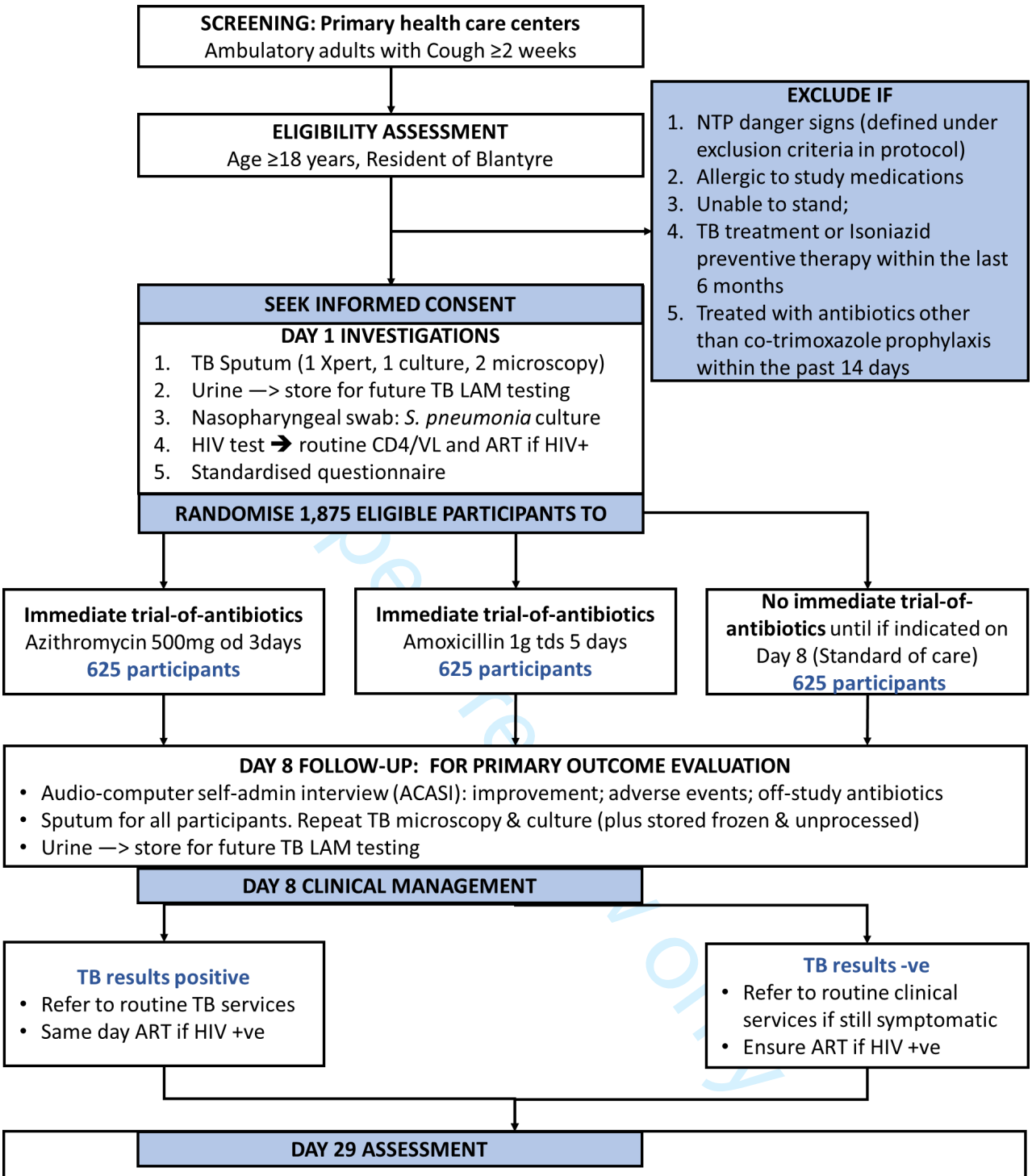


Figure 1: Flow diagram for the planned clinical trial in Blantyre, Malawi

3 Introduction

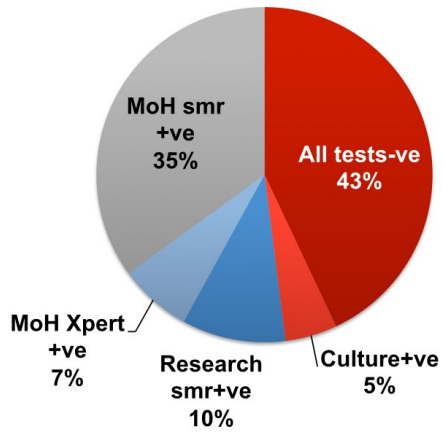
3.1 Background

Antimicrobial resistance is a growing crisis, becoming in 2016 one of only four health topics ever to be discussed at the United Nations General Assembly.[1-4] Tuberculosis is the leading global infectious cause of death in adults,[5] with approximately 10.4 million cases and 1.8 million deaths in 2015.[6] The high case-fatality rate in part reflects suboptimal diagnostics(Figure 2).[7-10]

Diagnosis method	Percentage
Mycobacteriology	57%
Clinical	43%

A. WHO annual TB notifications (WHO 2017 TB Report)

B.



Nliwasa et.al

Figure 2: method of diagnosis for TB notifications globally (A) and in Blantyre, Malawi (B)

To complement the suboptimal diagnostics, standard diagnostic algorithms in resource-limited settings include a “trial-of-antibiotics” (Figure 3). This is a course of broad-spectrum antibiotics, with negligible *Mycobacterium tuberculosis* activity, given to patients with symptoms such as cough in order to “rule-out” or “rule in” tuberculosis.[11-13] Patients with negative sputum mycobacteriology and responded to antibiotic treatment are considered tuberculosis negative while those who remain symptomatic are deemed likely to have tuberculosis and undergo further evaluations leading on to receiving tuberculosis treatment.

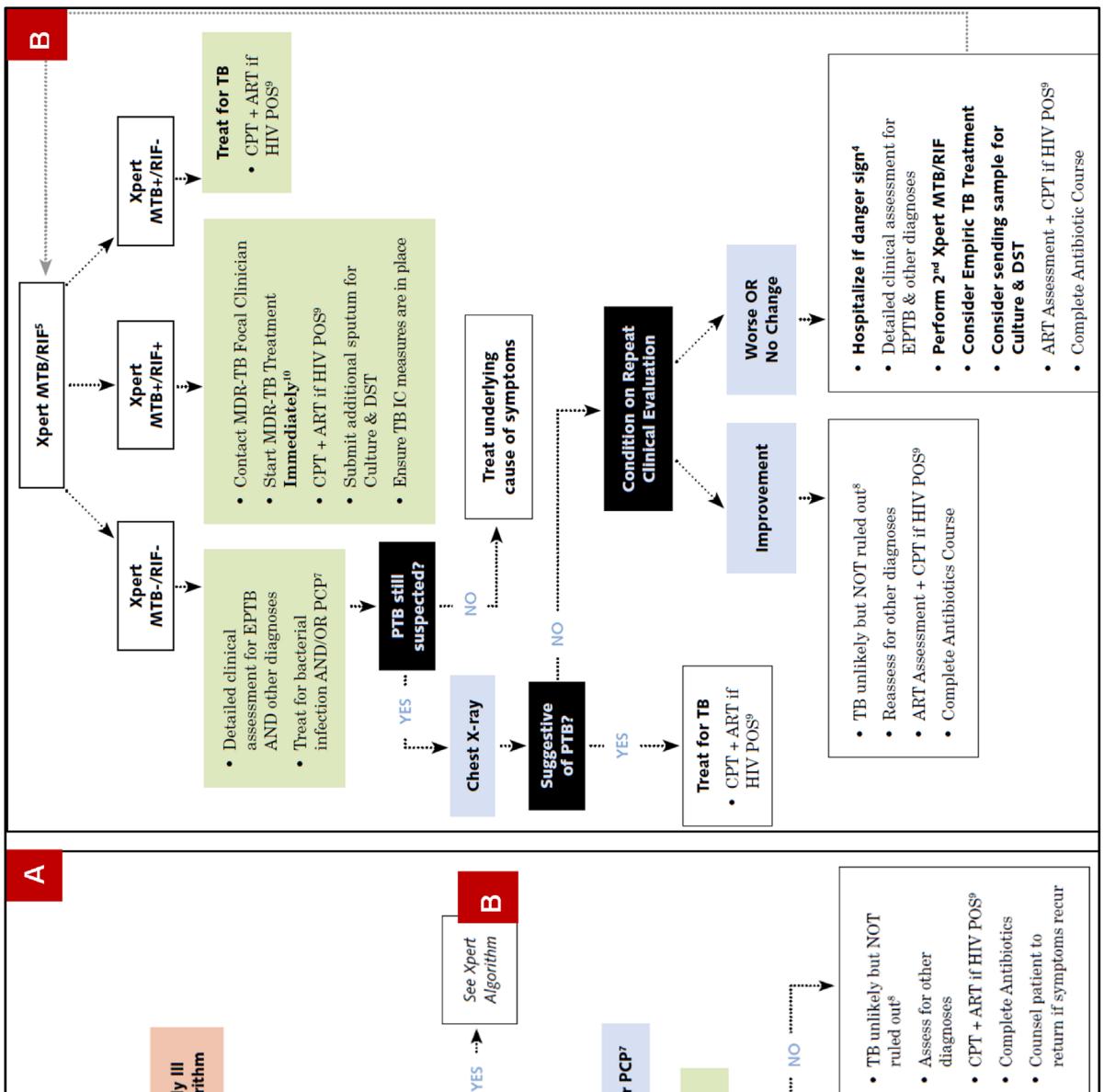


Figure 3: Implementation of trial-of-antibiotics (marked with red boxes) in Malawi TB diagnostic algorithm, National TB control program (NTP)

Approximately 26.5 million course of antibiotics are prescribed in the diagnosis of the 5.3 million smear negative tuberculosis registrations per annum (Figure 4).[6] This estimate is based on an average of 5 antibiotic courses per sputum-negative treatment initiation, with 2 courses given to the patients before tuberculosis treatment,[8] and the other 3 courses accounting for patients whose symptoms resolved and tuberculosis was ruled out.[14].

Wilkinson et al[14] prescribed 120 + 74 courses of trial-of-antibiotics to diagnose 40 smear-negative TB patients (a typical ratio of ~1:5).[8] If generalizable, then for 5.3 million annual smear-negative TB registrations globally ~5 x 5.3 million trial-of-antibiotics courses (26.5 million) will have been prescribed.

Enrolled	**280**	
TB smear microscopy positive		160
Given trial-of-antibiotics (amoxicillin)	**120**	
Improved, declared TB negative		46
Given trial-of-antibiotics (erythromycin)	**74**	
Improved, declared TB negative		34
Treated for smear negative TB	**40**	

Wilkinson et.al Int J Tuberc Lung Dis. 2000

Figure 4: Quantifying number of trial-of-antibiotics courses prescribed per year using data from Wilkinson et.al and WHO TB Report 2016

Despite this widespread use, there is no randomised controlled trial evidence supporting the diagnostic accuracy of trial-of-antibiotics. There is also a dearth of evidence on their impact on antimicrobial resistance or patient clinical outcomes.

3.2 Systematic literature review

We performed a systematic literature review to determine the sensitivity and specificity of using a trial-of-antibiotics compared to sputum mycobacteriology for diagnosis of PTB. We also wanted to describe how trial-of-antibiotics tits into TB diagnostic algorithms: timing of prescription; type, duration, and number of antibiotic prescriptions; and how response to treatment is measured. We searched MEDLINE, Embase, and Global Health using the Ovid platform to identify studies meeting the following criteria:

Population	Adult patients with symptoms suggestive of pulmonary tuberculosis
Intervention	Routinely prescribed broad-spectrum oral antibiotics without MTB activity, and given as part of evaluation of pulmonary TB
Outcome	sensitivity and specificity of the intervention in comparison with any mycobacteriology test
Study design	Any design with prospective component allows evaluation of the outcome of the intervention
Time frame	Studies published after WHO declaration of TB as a 'global emergency' (1993)
Language	English, lack of translation capacity

We identified 7,064 articles from a systematic search on MEDLINE, Embase, and Global Health using the Ovid platform. Of these studies, 12 were eligible for narrative synthesis and seven had suitable data for meta-analysis. None of the studies was an RCT and all the observational studies were small and not primarily designed to address the benefits and consequences of trial-of-antibiotics. Unlike our proposed RCT, most of the published work was from hospital setting or in specialised clinics. Most studies used amoxicillin and some studies prescribed a subsequent course of antimicrobials either before or after assessing for improvement. The definition of improvement from baseline clinical state was largely subjective: it was based on self-report, clinical examination, radiological assessment or a combination.

There is no consensus on the sensitivity and specificity of trial-of-antibiotics across studies with estimates ranging from 43% to 91% for sensitivity and 41% to 82% for specificity (shown below).

Population, Study		Sensitivity, 95% CI			Specificity, 95% CI		
237	Wilkinson et al 1997	0.5	0.37	0.64	0.82	0.76	0.87
120	Wilkinson et al 2000	0.83	0.71	0.91	0.56	0.44	0.67
204	Kudjawu et al 2006	0.91	0.83	0.96	0.65	0.56	0.73
1000	Kamran et al 2006	0.72	0.62	0.8	0.41	0.38	0.44
264	Soto et al 2011	0.43	0.32	0.55	0.68	0.63	0.72
439	Soto et al 2013	0.46	0.34	0.58	0.6	0.53	0.66
440	Padmapriyadarsini et al 2	0.7	0.55	0.8	0.69	0.64	0.73

We could not identify any RCT, the current literature only has small studies, with trial-of-antibiotics not being the primary focus of investigation in most cases. There is limited data for primary care settings as most of the work was in hospital setting. None of the studies addressed AMR. Therefore, despite widespread use, the approach, the value and consequences of having trial-of-antibiotics in TB diagnostic algorithms, remains to be established.

3.3 Planned study

To address the evidence gaps related to a) accuracy, b) antimicrobial resistance, and c) impact on clinical outcomes), we propose to conduct a randomised controlled clinical trial recruiting adult patients presenting to primary care centres in Blantyre, Malawi with history of cough for at least 2 weeks. After excluding those with danger signs we will randomise participants to receiving or not receiving trial-of-antibiotics (azithromycin or amoxicillin) from Day-1 to determine diagnostic accuracy (specificity) against mycobacteriology reference standard (smear microscopy, Xpert/MTB/RIF and culture).

For secondary outcomes, we will also compare between arms differences in antimicrobial resistance and clinical outcomes (risk of death, hospitalisation, and missed TB diagnosis) at Day-29. To our knowledge this will be the first randomised controlled trial to address these questions in over 20 years of systematic use of trial-of-antibiotics without strong evidence base.

3.4 Rationale for current study

3.4.1 Accuracy of trial-of-antibiotics

As an approach that is being used on such a large scale, trial-of-antibiotics should ideally have a strong evidence-base (supported by reference mycobacteriology) of how much diagnostic and/or clinical improvement it brings to the TB diagnostic algorithm.[15,16] This will be among the most important considerations when deciding whether it is worth the trade-off with potential for AMR. Such evidence could come from an RCT or a well-designed prospective study.[15-17] However, despite being in use for more than 20 years, we have not identified any such clinical trial, and even the observational evidence is highly limited and of insufficient quality and quantity to definitively address the question.

There is also no guidance on antibiotic choice beyond a recommendation to avoid those with anti-tuberculosis activity (like fluoroquinolones). Another key area that lacks clarity is lack of a clear definition for clinical resolution when determining the outcome of trial-of-antibiotics. Clinical resolution is the basis for decisions that follow (i.e. discontinue follow up or proceed Antimicrobial resistance and trial-of-antibiotics

Antimicrobial resistance can be either intrinsic or acquired. The risk of acquired resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been previously investigated, although previous work has shown that empirical antibiotics can drive rapid emergence of AMR.[18,19] For example, co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010.[20] Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniae*, but with increased macrolide-resistance 6 months later.[21,22]

In our study, the AMR risks of empirical antibiotic prescriptions (azithromycin and amoxicillin arms of the RCT) are justified because of the widespread use of this approach for amoxicillin, and the low potential clinical impact and short-lived effects of use of azithromycin on AMR, given the limited use of macrolides in Malawi. Mathematical modelling work suggests that macrolide resistance can successfully be eliminated by intra-species competition alone (fitness cost) within 5 years of last use.[23]

3.4.2 Antimicrobial resistance and trial-of-antibiotics

Antimicrobial resistance relating to antibiotic use during evaluation for suspected tuberculosis has not been investigated before. Previous work has shown that empirical antibiotics can drive rapid emergence of antimicrobial resistance.[18,19] Co-trimoxazole prophylaxis for HIV-positive patients, introduced in 2005, was followed by near-universal resistance in bloodstream infections by 2010[20] also shown in Table 1. Mass drug administration of azithromycin for trachoma control initially reduces nasopharyngeal carriage of *Streptococcus pneumoniae*, but with increased macrolide-resistance 6 months later.[21,22]

We will investigate antimicrobial resistance in nasopharyngeal *S. pneumonia* by randomisation arm and cumulative antibiotic exposure to assess the extent to which brief exposure drives antimicrobial resistance during diagnostic work-up for tuberculosis. An ecological niche for many bacterial species, the upper respiratory tract also presents a convenient window for investigating antimicrobial resistance.[24] *S. pneumonia* is the organism of choice not only for being an important cause of respiratory tract infections but also because it often colonises the upper respiratory tract and has well documented laboratory investigation procedures in place.[25] As exploratory analyses, we will also assess nasopharygeal colonization and antimicrobial resistance in relation to tuberculosis treatment and HIV status.

Table 1 Resistance patterns of common aetiologies of pneumonia to commonly used antimicrobials in Blantyre, Malawi

		Gram positive		Gram negative			
Organism		Streptococcus pneumoniae	Staphylococcus aureus	Haemophilus influenzae	Klebsiella pneumoniae	Escherichia coli	Pseudomonas aeruginosa
Prevalence		15.6%	6.6%	0.9%	4.4%	0.1%	1.5%
Resistance percentage	amoxicillin	*	*	58%	100%	94%	100%
	penicillin	21%	*	*	*	*	*
	co-trimoxazole	98%	40%	100%	92%	94%	75%
	chloramphenicol	21%	2%	92%	48%	61%	100%
	Erythromycin	2%	30%	*	*	*	*
	tetracycline	38%	35%	*	*	*	*
	Ceftriaxone	*	*	0%	90%	30%	100%
	Ciprofloxacin	*	*	NA	705	31%	24%

*not routinely tested

2016 data from hospitalised febrile patients at Queen Elizabeth central hospital (Blantyre, Malawi) as reported by the MLW Clinical research laboratory (unpublished).

3.4.3 Potential benefits of antibiotics

In areas with high HIV prevalence, empirical antibiotics during tuberculosis investigations could be life-saving: mortality immediately before and after tuberculosis diagnosis is high, [7,26] and is often secondary to severe bacterial infections.[26-28] The leading aetiologies of infection and death on tuberculosis treatment as well as among outpatients with tuberculosis-like symptoms are *Streptococcus pneumoniae* and non-typhoidal salmonellae (NTS): both can present with cough (primary cause) or as co-morbidities (super-infections) in patients presenting with active *Mycobacterium tuberculosis* (*M.tb*) disease.[26-28] If effective treatment of this type of life-threatening primary/super-infections reduces mortality during the diagnostic work-up of suspected TB in people living with HIV (PLHIV), then empirical use of broad-spectrum antibiotics would be indicated for this purpose alone, irrespective of any diagnostic contribution to TB treatment decisions. In this context, azithromycin may be the most effective arm, as Salmonella infections are highly sensitive to azithromycin, but not to amoxicillin.[29]

3.4.3.1 Measures of clinical benefit of trial-of-antibiotics

In this study, we will investigate the overall clinical benefit of trial-of-antibiotics by comparing the risk of any of death, hospitalisation, and missed TB diagnosis by Day 29. Although all these events are potential consequences of trial-of-antibiotics, grouping them as a single composite endpoint may only appropriately represent the effect of the intervention 1) there are similarities in the importance patients would attach to each of its components and 2) the components occur with similar frequencies in the patient population.[30]

The impact of antibiotics on hospitalisation and mortality causing illnesses is as described above. Both these outcomes are important with their similarity hinged on the fact that hospitalisation event predicts mortality. In patients with chronic cough, frequencies of mortality and that of hospitalization over a two months period are similar, ranging from 2 to 6%.[31]

TB misdiagnosis becomes a concern because of the potential for misclassification in either direction –false positive or false negative. False positive diagnosis in the context of trial-of-antibiotics would occur when the underlying pathology for the respiratory symptoms is not responding to the antibiotic, which can be secondary to either AMR or the illness not being of bacterial origin. On the other hand, patients would be prone to a false negative result had both TB and a susceptible bacterial infection. If the symptoms were largely driven by the susceptible bacterial infection, their symptoms will improve and would be declared TB negative. TB is a life-threatening illness, missing its diagnosis can therefore lead to death which is more important to an individual patient than taking TB chemotherapy with a false positive TB diagnosis. We will therefore include only missed TB diagnoses in the composite clinical outcome. Unpublished data from Blantyre shows that the frequency of missed TB diagnosis under routine care settings is approximately 5% which is similar to that of death and hospitalisation.

3.4.4 Important subgroups

Response to trial-of-antibiotic- in patients with bacteriologically confirmed tuberculosis (i.e. false-negatives/low sensitivity from the perspective of TB diagnosis) may relate to multiple super-infections and so this phenomenon may vary by HIV status, since multiple concurrent infections are a hallmark of advanced HIV immunosuppression, and commonly identified in patients with suspected TB in the pre-ART era.[8,27] More recently, in Malawi, 45% of adults who presented to primary care with prolonged cough (≥2 weeks) were HIV-positive, of whom only ~20% started TB treatment on the basis of positive mycobacteriology.[31] As such, the benefits and consequences of trial-of-antibiotics may vary by HIV status and by subsequent TB treatment decisions. We will, therefore, include a pre-specified sub-analysis of trial outcomes stratified by HIV and ART status.

3.5 Choice of study interventions

Our trial will compare azithromycin and amoxicillin to standard of care. We propose 2 different antibiotic arms for the following reasons: -

a) Macrolides, including azithromycin, are rarely used in Malawi because of their higher manufacturing costs. However, they do provide a more effective treatment of community-acquired pneumonia than the standard antibiotic by Ministry of Health for trial-of-antibiotic (amoxicillin), because of low levels of acquired macrolide-resistance in bacterial isolates in Malawi,[29] reflecting low rates of past exposure to this class of drugs, and also better intrinsic coverage of "bacterial cause of pneumonia including "atypical" intracellular organisms such as *mycoplasma* species.

Although viral pneumonias, *Pneumocystis jiroveci* (PCP) and non-infectious causes of cough will still not be expected to respond to azithromycin, this arm should then provide the highest possible diagnostic discrimination for bacterial vs mycobacterial causes of cough. The starting point of low pre-existing (acquired) resistance will also facilitate investigation of AMR acquired during trial-of-antibiotics. However, the trial will have limited national relevance in Malawi without comparison to an antibiotic in programmatic use.

b) Amoxicillin is low cost option that is still a recommended treatment for community-acquired pneumonia in most settings, including UK, despite potential treatment failure from bacterial pneumonia due to organisms with intrinsic ("atypicals") or acquired (common in gram-negative organisms, and *Staphylococcus aureus*) penicillin resistance.[29] This arm reflects the true standard of care (SOC) currently in widespread use in Malawi and many other low-income countries, and so provides data of immediate programmatic relevance and also a starting point to investigate exacerbation of pre-existing AMR pressure. If there is a marked difference between the azithromycin and amoxicillin arms, then there will also be important health economic considerations of relevance to many national TB programmes beyond Malawi.

Azithromycin provides effective treatment for community-acquired pneumonia[32-34] and has negligible activity against *M.tb.*[35,36] As discussed above, macrolides are not commonly used in Malawi. Azithromycin has an excellent safety profile and is used for mass drug administration (MDA) in communities prone to trachoma. Azithromycin used for MDA in Ethiopia reduced inter-current infections[21,37] and death in children,[38,39] supporting the safety of using this drug for our trial.[7]

Amoxicillin is the first line treatment for outpatient management of pneumonia in Malawi and is commonly used for trial-of-antibiotics. We anticipate higher specificity for azithromycin than amoxicillin, due to broader coverage of "atypical pneumonia" organisms, and salmonella species,

but with the 2 antibiotics arms having “equipoise” due to lack of previous head-to-head comparison.[27]

3.6 Nasopharyngeal pneumococcus for AMR

Streptococcus pneumonia is a major cause of morbidity and mortality in children and adults.[20,29,40,41] Asymptomatic nasopharyngeal carriage of *S. pneumoniae* is common and a prerequisite for the occurrence and transmission of invasive pneumococcal disease.[42,43] Since carriage is more common than the invasive *S. pneumoniae* disease it forms a basis for establishing circulating serotypes, resistance patterns, and evaluation of vaccine effectiveness.

The other key advantage is the existence of globally accepted laboratory procedures for assessing and interpreting pneumococcal resistance. Our laboratory (in Malawi-Liverpool Wellcome Trust) has carried out pneumococcal work for decades with outstanding quality assurance reputation.

3.7 Objectives and outcomes

In Table 2 below, we present study objectives together with corresponding outcomes. We have clarified the outcomes with detailed definitions and planned analyses under “statistical approach” section.

Table 2: study objectives and outcomes

Objective	**Outcome**
Primary	
1. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in adults with prolonged cough (and have a valid sputum test result) at primary care level in Malawi.	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among participants with a valid result from at least one sputum test
2. To determine the overall clinical benefit of giving empirical antibiotic treatment in primary care participants with chronic cough.	Proportion of participants experiencing at least one of the following adverse outcomes by Day 29: 1) death 2) hospitalisation 3) missed TB diagnosis

Secondary	
3. To evaluate using nasopharyngeal Streptococcus pneumonia, the effect of a trial-of-antibiotics on selection for antimicrobial resistance.	Proportion of Day 29nasopharyngeal *Streptococcus pneumoniae* isolates resistant to any of commonly used antimicrobials.
4. To establish the diagnostic value of trial-of-antibiotics for excluding pulmonary tuberculosis (PTB) in primary care presenting Malawian adults with prolonged cough including those without a successful sputum test (unable to submit sputum and those with invalid sputum results).	Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology reference standard, among all randomised participants, with those who could not provide sputum or had an invalid sputum result classified as mycobacteriologically negative.
5. To estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other.	• Incremental cost per quality adjusted life year gained • Total direct medical costs per participant over 56 days • Eq-5D utility score
Exploratory	
Our exploratory analyses will be comparisons between the azithromycin and amoxicillin arms for all our primary and secondary outcomes.	

4 Study design, participants, and statistical approach

4.1 Study design

This is a three arm (625 per arm) individually randomised (1:1:1), open-label controlled clinical trial investigating accuracy and broader clinical, and antimicrobial resistance impact of using trial-of-antibiotics to "rule out" tuberculosis among adults presenting with cough at primary care centres in Malawi.

4.2 Study setting

We will screen adults aged at least 18 presenting to primary care centres in Blantyre, Malawi. Blantyre has an estimated adult HIV prevalence of 12.7% (95% CI: 11.9 to 13.6) and an estimated tuberculosis prevalence of 1,014 per 100,000 (95% CI: 486 to 1,542).[44]

4.3 Standard of care

The standard of care in national guidelines from the NTP for primary care patients presenting with cough and are otherwise well (no danger signs) is to take sputum x 2 for smear microscopy or Xpert and ask them to return for results, typically 3 days - 1 week later (Figure 3 and 5). The Malawi tuberculosis diagnostic algorithm recommends use of broad-spectrum antibiotics as trial-of-antibiotics after negative sputum tests are provided to the patient, if they remain symptomatic.

However, more commonly this algorithm is adapted in the outpatient setting to combine prescription of antibiotics (usually amoxicillin) with sputum collection at the first visit, to save the patient from making separate visits: thus, our amoxicillin arm is the most common standard-of-care in Malawi, while the no-antibiotic arm is the NTP recommended standard-of-care.

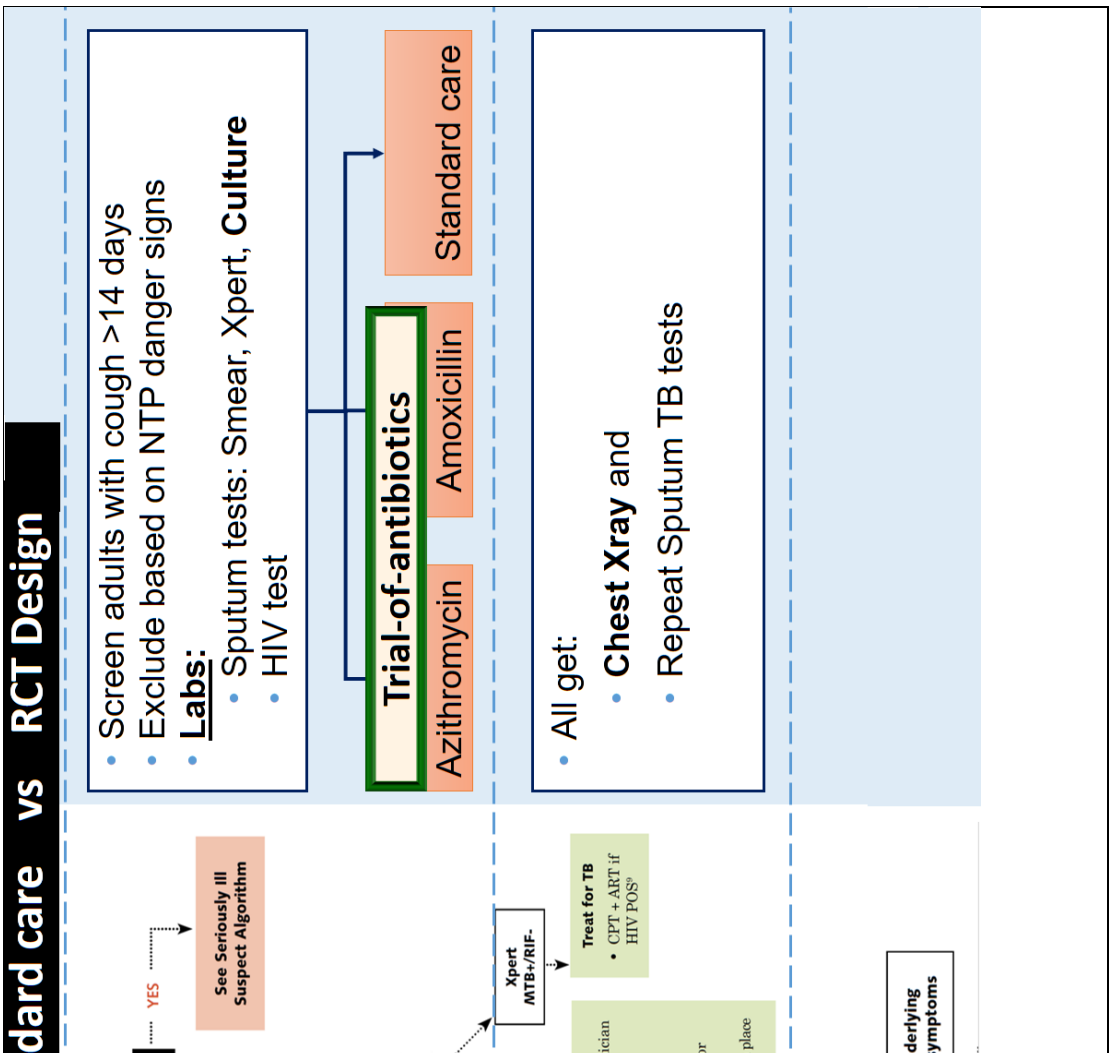


Figure 5: A comparison of standard of care (Malawi NTP guidelines) and the RCT design with respect to timing of trial-of-antibiotics and study procedures

4.4 Eligibility criteria

We will offer enrolment to patients who satisfy the following inclusion and exclusion criteria.

4.4.1 Inclusion Criteria

- Ambulatory clinic attendees presenting with cough for at least 14 days
- No previous formal consultation for current illness (initial presentation)
- Aged at least 18 years
- Reside in Blantyre and willing to return to the same clinic for follow up visits over the entire study period.

4.4.2 Exclusion Criteria

- Self-reported allergy to study medications
- Danger signs (WHO/Malawi NTP): respiratory rate > 30/min, temperature >39^{o}C, Heart rate >120/minute, confused/agitated, respiratory distress, systolic blood pressure <90 mmHg, inability to walk unassisted
- Treated with antibiotics other than co-trimoxazole prophylaxis within the past 14 days
- TB treatment or Isoniazid preventive therapy within the last 6 months

4.5 Interventions

We will have two active study arms receiving trial-of-antibiotics at enrolment (azithromycin and amoxicillin) and a standard of care arm of no trial-of-antibiotics. In this study, the goal is to investigate the role of these antibiotics as they are used in TB diagnostic algorithms, as "trial-of-antibiotics," to exclude TB in symptomatic patients. The study is likely to be underpowered to detect differences between the 2 antibiotic arms will only be compared for exploratory outcomes.

4.5.1 Name and description of intervention arms

The study will have three arms as follows:

- Arm 1: Immediate trial-of-antibiotics with Azithromycin 500mg once daily for 3 days.
- Arm 2: Immediate trial-of-antibiotics with Amoxicillin 500 mg 3 times daily for 5 days.
- Arm 3: Standard of care

4.5.2 Legal status of drugs used in intervention arms

Both azithromycin and amoxicillin are registered for use in Malawi and United Kingdom, with both Arms 1 and 2 regimens being UK-recommended community-acquired pneumonia treatment.

4.5.3 Summary of Product Characteristics

Appendix 3 includes current versions of package insets for azithromycin and amoxicillin. We will review and update (when applicable) the package inserts annually with each ethics continuing review.

4.5.4 Drug Storage and Supply

We will procure study products from Durbin PLC (DURBIN PLC 180 Northolt Road South Harrow Middlesex HA2 0LT). Azithromycin will be manufactured by Sandoz limited or other pharmaceutical companies recognised in United Kingdom where Durbin is based. Amoxicillin will be manufactured by Medopharm private limited or other pharmaceutical companies recognised in United Kingdom where Durbin is based. Both azithromycin and amoxicillin are stable at room temperature. We will therefore ship and store in ambient conditions.

4.5.5 Preparation and labelling of study drugs

Study products will be stored at Malawi Liverpool Wellcome Trust Pharmacy. The pharmacy team will be responsible for packing and labelling.

4.5.6 Known drug reactions (adverse events)

Azithromycin and amoxicillin are already widely used in Malawi and are well tolerated. Rare side effects for azithromycin include nervousness, dermatologic reactions including Stevens–Johnson syndrome, anaphylaxis and prolonged QT interval. Rare side-effects for amoxicillin are mental state changes, light-headedness, photosensitivity and severe allergic reactions.

4.5.7 Concomitant medication and interaction with other therapies

We do not have any restrictions with respect to concomitant medications apart from those listed in the exclusion criteria. We expect some participants to be on HIV antiretroviral drugs and some may subsequently start tuberculosis therapy. Important interactions therefore would be those with HIV antiretroviral drugs and tuberculosis therapy. There is no moderate or major interaction between either azithromycin or amoxicillin with the classes of HIV antiretroviral drugs, tuberculosis therapy, and antimalarial drugs used in Malawi.

4.5.8 Trial restrictions

We do not require participants to have any dietary restrictions. We will also accept co-administration with contraception. Our trial interventions can safely be used in pregnancy, so we will include pregnant women should they be eligible.

4.5.9 Assessment of compliance

On Day-8, we will document self-reported compliance adherence of study products.

4.5.10 Withdraw of interventions

The investigator may also terminate a participant from study product if indicated by an adverse reaction. If a participant stops taking study product either voluntarily or by investigator decision, they will be encouraged to remain in follow up and their data will form part of intention to treat analyses.

4.6 Statistical approach

We will summarise the processes of recruitment including non-eligibility and reasons of exclusion in a CONSORT flow chart. We will describe the study participants by their baseline characteristics which we will report for each arm. We will perform analyses of all our outcomes based on an intention to treat analysis (using the arm patient was randomised to), adjusting for centre. We will make the following comparisons:

i) azithromycin or amoxicillin versus standard of care

ii) azithromycin versus standard of care

iii) amoxicillin versus standard of care

We will perform data cleaning and analysis using Stata release 15 (Stata Corp, College station, Texas, USA).

The following are descriptions of each outcome and corresponding statistical approach. The statistical approach will be expanded in a detailed statistical analysis plan, separate to the protocol, which will be finalised before unblinding the study data.

4.6.1 Primary outcome

The clinical trial has two separately powered, and distinctly assessed primary outcomes, one for diagnostic evaluation (Primary outcome 1: Day 8) and the other for clinical impact (Primary outcome 2: Day 29) of the intervention.

4.6.1.1 Primary outcome 1: Specificity of day 8 symptom change versus mycobacteriology

Investigational test

The investigational test is change in symptoms at Day 8 categorised as: improved or not improved (no change plus worsened) in response to the following question: *on day 1, you reported that you were unwell; compared to that day, has your illness worsened, remained the same, or improved?*

To minimise ascertainment bias in ascertaining this endpoint, the evaluation of improvement of baseline symptoms will be captured using a self-interview platform: Audio Computer Assisted Self-Interview (ACASI). After orientation, the participant will be left alone in the room to interact with the

computer. ACASI on Day-8 will precede all other interaction with research staff and clinical assessment/decision making. We will report ACASI interview outcome as:

- **ACASI-test-negative** if the participant reports improvement
- **ACASI-test-positive** if the participant reports no change or worsening.

Reference test

Mycobacteriology reference standard will be defined in participants with at least one specimen with a valid result on days 1 and 8 as:

- **Sputum-test-positive**: if at least one positive smear microscopy, Xpert/MTB/RIF, or MTB culture on sputum samples taken.
- **Sputum-test-negative**: none of the day 1 and day 8 sputum samples are positive on smear microscopy, GeneXpert MTB/RIF, or MTB culture.

To minimise bias, the mycobacteriology will be performed by a high-quality research laboratory in the University of Malawi College of Medicine by staff with no access to participant treatment allocation information or ACASI results.

The diagnostic assessment outcome

- Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 ACASI against a mycobacteriology reference standard (b+d in Figure 6). Using the investigational test and reference test described above, this can be rewritten as: proportion of sputum-test-negative participants who are ACASI-test-negative.

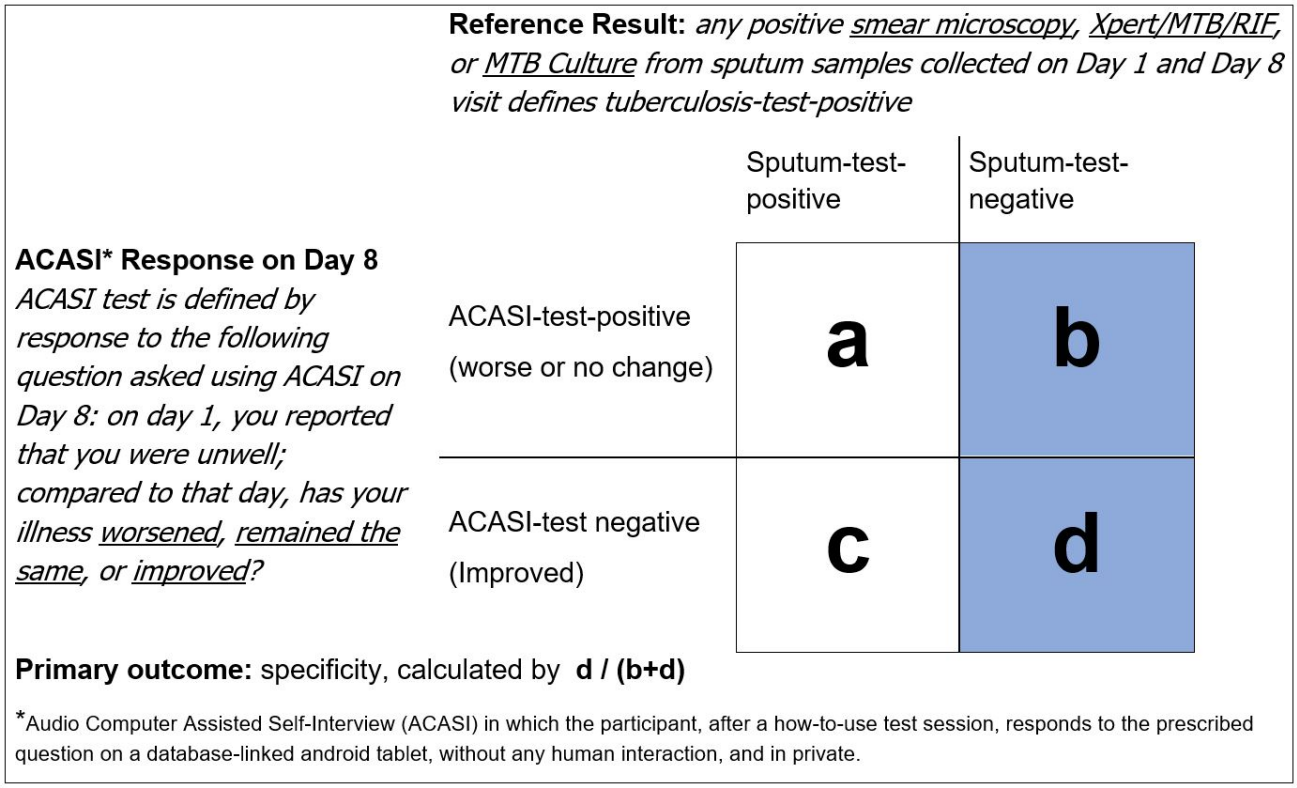


Figure 6: Ascertainment of diagnostic value of trial-of-antibiotics

Estimation of measures of effect

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for center. For each comparison, we will report 95% Confidence Intervals and Chi-square p-values. In pre-specified subgroup analysis, we will estimate the treatment effects stratifying by baseline HIV status. If the GLM model does not converge, we will use logistic regression to estimate the treatment effect using an odds ratio.

Participants without valid sputum mycobacteriology results

Primary analyses will be limited to participants who have at least one valid sputum sample result from all samples collected on visits Day-1 and Day-8. However, in real-life, ~15% fail to produce sputum, we will as a secondary outcome, perform all the analyses described for primary outcome with these participants defined as mycobacteriology negative. Further sensitivity analyses with urine lipoarabamannan antigen (LAM) results will include them in mycobacteriology definition.

4.6.1.2 Primary outcome 2: Clinical benefit of trial-of-antibiotics

Outcome definition

Proportion of participants experiencing at least one of the following adverse outcomes: death, hospitalisation, and missed TB diagnosis. The definitions of the components of this composite clinical outcome are defined in the table below:

Outcome component	Definition
death	Proportion of deaths by Day 29
hospitalisation	Proportion hospitalised for any cause by Day 29
missed TB diagnosis	Day 29 proportion of participants meeting standard **mycobacteriological and radiological** TB definitions but incorrectly classified as TB negative and not yet on TB treatment by Day 29.

Estimation of measures of effect

We will use a generalised linear model (GLM) with identity link to estimate risks differences and the GLM with log link to estimate risk ratios for the three comparisons, adjusting for primary care center. For each comparison, we will report 95% Confidence Intervals and Chi-square p-values. If the outcome is rare or if GLM does not converge, we will use logistic regression to model odds and report odds ratios for the following comparisons and their associated report 95% CIs and p-values.

4.6.2 Secondary outcomes

Outcome definitions

1) Proportion of day 29 nasopharyngeal *Streptococcus pneumoniae* isolates resistant to any of the commonly used antimicrobials.

We will define **AMR positive** as having nasopharyngeal isolates of Streptococcus pneumoniae that are resistant to any of the following commonly used antibiotics: ceftriaxone, amoxycillin, cefoxitin, azithromycin, and erythromycin as determined using disc diffusion technique; and **AMR negative** as either (1) not isolating any Streptococcus pneumoniae or (2) isolating any Streptococcus pneumoniae that is not resistant to any of the assessed antibiotics. For each arm, and at both baseline and day 29, we will report proportion of AMR positive participants. The study outcome will be the proportion of AMR positive participants at day 29.

2) Proportion of participants correctly classified as PTB negative based on report of improvement of baseline symptoms on study Day-8 (i.e. after a trial-of-antibiotics if in azithromycin or amoxicillin arms, or without antibiotics if in standard of care arm) against a mycobacteriology

reference standard, among all randomised participants, with those who do not have a valid sputum test result classified as mycobacteriologically negative.

Estimation of measures of effect

Our secondary outcomes are anticipated to be rare, we will therefore use logistic regression to model odds and report odds ratios for the following comparisons and their associated report 95% CIs and p-values.

4.6.3 Exploratory outcome

Our exploratory analyses will be comparisons between the **azithromycin** and **amoxicillin** arms for all our primary and secondary outcomes.

4.6.4 Planned subgroup analyses

We will perform subgroup analysis for the primary outcome. The important subgroups based on rationale detailed under section 2.4.4, include HIV status, ART status, and PTB treatment. HIV and ART status will be as documented on Day-1 while PTB treatment will be either as:

- TB treatment commenced based on positive baseline (Day-1 and Day-8) mycobacteriology, *or*
- TB treatment commenced within 29 days of enrolment in patients with negative Day1 and Day-8 bacteriology.

The 29 days cut off for clinical decision to treat is to ensure that we only capture TB disease that was present at baseline. 29 days is a reasonable because: TB is a slowly progressing disease which if positive at Day-29, must have been incident on Day-1; and in routine care setting it can take over a month from presentation to diagnosis of TB.[8]

4.7 Sample size and power

4.7.1 Primary outcome 1: specificity of day 8 symptom change versus mycobacteriology

We assume that trial-of-antibiotics (in azithromycin arm or in amoxicillin arm) will correctly classify 60% of mycobacteriology negative participants.[14] We have determined that 400 mycobacteriologically negative (true negatives) participants per arm will provide 80% power to detect a 10% difference in proportion of participants correctly classified as negative by amoxicillin arm or by azithromycin arm (60%) versus standard of care arm (50%). See table 3. We assume that 80% of participants randomised will have negative mycobacteriology,[31] requiring 500 participants to yield the 400 per arm. Assuming that 15% will not be able to produce sputum, and that 5% will not return for Day-8 visit, the sample size is increased to 625 per arm or 1,875 for the whole study.

For a 2:1 comparison (combining the two antibiotic arms versus the standard of care arm), 305 sputum-test-negative participants per arm will be needed to achieve 80% discriminatory power to detect a 10% difference in specificity. Accounting for TB prevalence, ability to produce and submit sputum, and loss-to-follow up increases the sample size requirement to 472 per arm or 1,416 for the whole study.

Table 3: Power and sample size estimation for primary outcome 1

True negatives (mycobacteriology tests negative participants) **b+d**	[1]**p (negatives correctly classified) d/(b+d)**	[2]**effect size**	**power (X^2 difference between independent proportions)**
320	0.60	0.10	69%
400	**0.60**	**0.10**	**80%**
480	0.60	0.10	86%

[1] specificity with either azithromycin or amoxicillin trial-of-antibiotics arms

[2]risk difference (azithromycin arm- standard of care arm)

4.7.2 Primary outcome 2: Incidence of adverse clinical outcome at Day-29

We will use a pilot study to determine the standard of care risk of at least one of death, hospitalisation, and missed TB diagnosis. The pilot study is described in section 5.0.

For now, we will assume that there is a 10% risk of experiencing this composite adverse outcome in the standard of care arm, and that loss to follow up by Day-29 will be 10%. With the sample size of 625 participants per arm (based on the primary outcome 1 sample size calculation), and alpha of 0.05, we will be able to detect the difference between intervention and standard of care with 80% power, if the risk in intervention arm is 6% or lower (Table 4). This estimate is applicable to the 2:1 comparison of the study arms.

Table 4: Sample size estimation for clinical benefit outcome

Participants per arm based on primary	**625**
10% loss to follow up by Day-29	562
Outcome risk in standard of care arm	0.10
Desired power	0.80
Alpha	0.05
Required intervention arm risk	**0.06**

4.7.3 Secondary outcomes

1) Incidence of resistant *S. pneumonia* on Day-29

Study arms will be compared based proportion of participants with resistant *Streptococcus pneumoniae* on day 29. We assume 10% loss to follow up by Day-29, and the rate of *S. pneumonia* isolation from nasopharyngeal swabs in this population is expected to be ~45% at Day-29. The sample size based on the primary outcome (625 per arm) will provides ~253 *S. pneumonia* isolates/arm. In the standard of care arm, with 10% risk of resistant isolates, this translates into 25 cases. For the intention to treat population (the randomised 625 participants/arm) in the standard of care arm the 21 cases of resistant isolates translate into 4% (25/625) risk. To detect a twofold change in odds of day 29 AMR risk with at least 80% power, alpha of 0.05, and using Pearson's Chi-squared test, we will need at least 431 and 553 participants per arm for the 2:1 and pairwise comparisons respectively.

4.7.4 Exploratory outcomes

We anticipate that our sample size will be enough for hypothesis generation around our exploratory objectives but may not be enough to provide discriminatory power for comparison of outcomes between arms.

5 Pilot study

This area of research has limited evidence to guide the precise determination of sample size and the practical aspects of the clinical trial making a pilot study an invaluable tool. We have identified the following as key knowledge gaps which require exploration using a pilot study:

1) Among the adult patients presenting to primary care centres with cough for at least 2 weeks what proportion gets antibiotics:

- **a.** before clinic presentation?
- **b.** on first clinic visit?
- **c.** on follow up clinic visit after mycobacteriology results?

2) Following antibiotic treatment, how do patients report their clinical response? What are the best questions to ask patients post-antibiotic treatment to determine if they have improved or not? How best can we deliver these questions via Audio Computer Assisted Self-Interview (ACASI)? How well do these responses correlate with mycobacteriology and radiology?

3) What is the best timing for nasopharyngeal swabs for evaluating AMR in patients who receive a course of antibiotics during TB investigations?

4) In the standard of care setting, what proportion of adult patients presenting to primary care centres with cough for at least 2 weeks experience the following adverse outcomes (as defined under the clinical benefit composite endpoint)?

- **a.** death
- **b.** hospitalisation
- **c.** missed TB diagnosis
- **d.** HIV care loss to follow up
- **e.** TB care loss to follow up

5.1 Specific objectives of the pilot study

1) To determine the proportion of adults with prolonged cough who

a. present to primary care having already had antibiotics for the index clinical complaints.
b. receive antibiotics before sputum mycobacteriology results at first presentation
c. receive antibiotics after negative mycobacteriology

2) To establish an objective way of documenting response to antibiotic treatment using Audio Computer Assisted Self Interview (ACASI). Assessing ACASI responses against clinical signs, outcomes of TB mycobacteriology and chest radiography.
3) To determine:
    a. the prevalence of *Streptococcus pneumonia*;
    b. the prevalence of resistant *Streptococcus pneumonia* isolates;
    c. the optimal specimen collection timing for evaluating impact of antibiotic use on prevalence of *Streptococcus pneumonia* isolates resistant to common antibiotics
4) To establish standard of care rates of the following adverse clinical outcomes:
    a. death
    b. hospitalisation
    c. missed TB diagnosis
    d. HIV care loss to follow up
    e. TB care loss to follow up

5.2 Population for the pilot study

This exploratory study will include up to 400 adult (≥18 years old) patients presenting to primary care centres with cough for at least 14 days. We will exclude patients not meeting the eligibility criteria of the clinical trial.

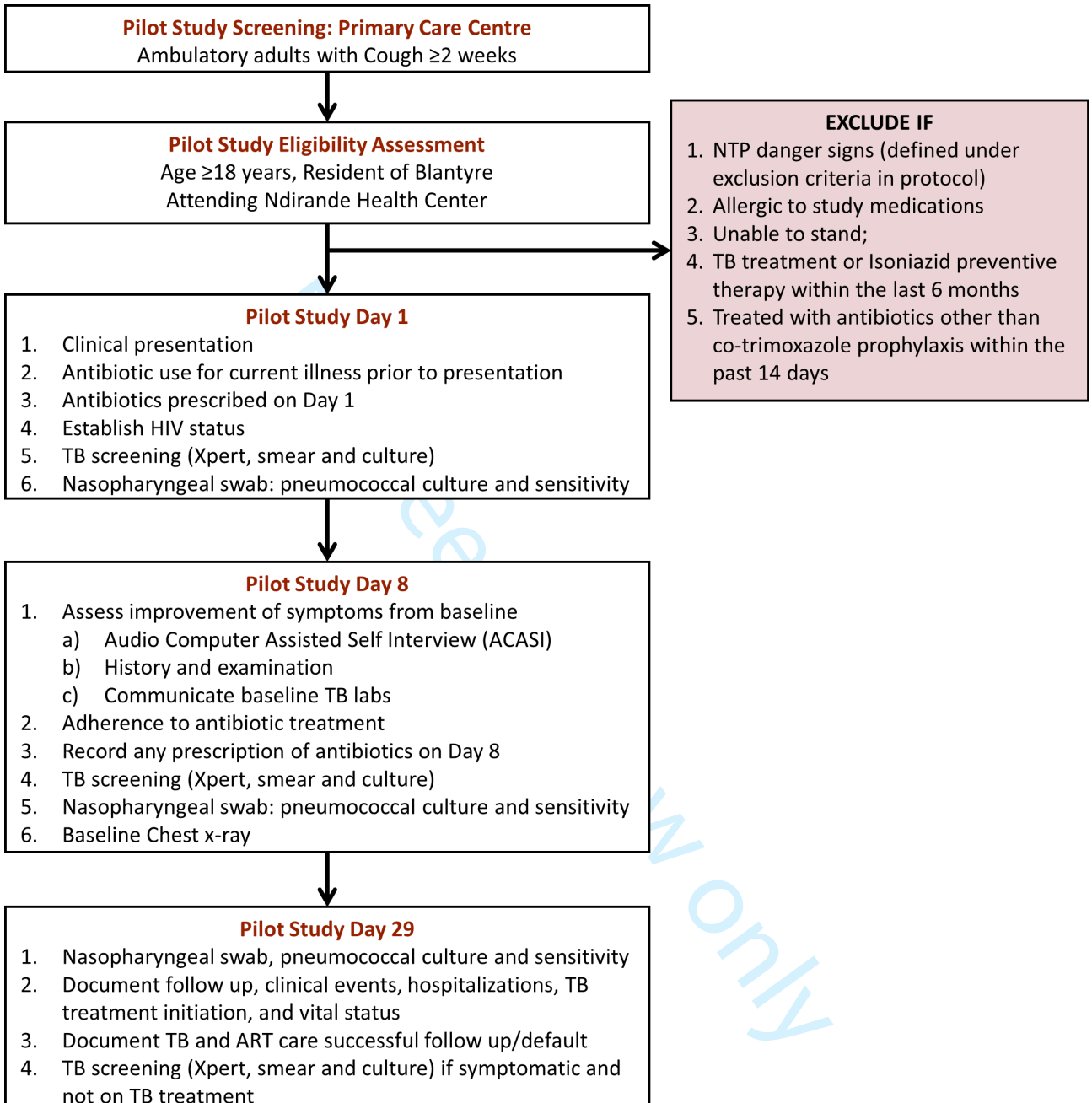
5.3 Pilot study procedures

The pilot study procedures are outlined in the flow chart below. Following pilot study informed consent, we will use a baseline assessment questionnaire to collect clinical history, and antibiotic use for the index illness prior to the clinic visit. Throughout follow up, we will record all antibiotic use from any source. We will collect sputum samples for mycobacteriology from all participants on Day1 and Day 8.

We will establish HIV and TB diagnosis throughout the study, link participants to care services, and follow their adherence to follow up. For TB we will use a combination of Xpert, smear and culture on Day 1, 8 and whenever symptomatic suggestions of TB arise. We will also perform a chest x-ray on Day 8 and a follow up film on Day 29.

We will collect nasopharyngeal swab samples, for antimicrobial resistance assessment using *Streptococcus pneumonia* culture and sensitivity, on Day 1, Day 8, and Day 29. We will assess change in symptoms and well-being from Day 1 to Day 8, by using various combinations of questions and answers delivered via Audio Computer Assisted Self Interview (ACASI) on Day 8. We

will ask participants which sets of questions they found easy to understand. We will also collect clinical information on all study visits including illness events, hospitalisations and vital status.



Pilot study flow diagram, summarizing the study procedures at each visit.

5.4 Data analysis

We will report the proportions of participants who used any antibiotics prior to primary care and during work-up for Tuberculosis. We will determine the best ACASI question and response combinations by participant reported ease of use, and by assessing correlation with clinical findings,

mycobacteriology and radiological outcomes. The optimal time for assessing AMR will be determined by comparing incidence of resistant *Streptococcus pneumonia* isolates at days 8 and 29.

We will comparing participants exposed to antibiotics to those not exposed to antibiotics by estimating and reporting relative risk and 95% confidence intervals for:

1) Day 8 and Day 29 of resistant Streptococcus pneumonia
2) Composite adverse outcome of experiencing any of: death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up

6 Study procedures

6.1 Screening

At the designated primary health care centres, study staff will approach patients with symptoms of pulmonary tuberculosis (including cough of any duration, fever, weight loss, and night sweats) with information about the study. Those willing to be screened for eligibility will be assessed against the study inclusion and exclusion criteria.

6.2 Informed consent

We will seek written informed consent (Appendix 1) from all patients who meet eligibility criteria before any trial-specific procedures. Screening for tuberculosis symptoms will not be considered as part of the study procedures, as it is already a fundamental component of the routine clinical assessment and history taking. A member of the study team will hand an informed consent form to a potential participant in their preferred language (Chichewa or English) detailing background, procedures, risks, benefits and participant expectations should they choose to join the study. The consent form will also state that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and no obligation to give reason for the withdrawal.

If they choose to join as a study participant, we will then request them to sign two copies of informed consent form. If a potential participant does not know how to read or write, we will perform the informed consent process in the presence of a witness. In such cases, if they agree to participate in the study, we will ask them to sign using a thumb-print in the presence of their witness and a study team member. We will keep one copy of the signed informed consent forms and hand the participant the other copy.

6.3 Baseline procedures

After consenting, we will on the same visit request participants to provide 2 on the spot sputum samples for smear microscopy, Xpert and culture collected at least one hour apart. Those unable to spontaneously produce sputum will be instructed in the physiotherapy manoeuvre of “huffing” (forced expiration technique) for inducing mucus clearance from the airways.

Patients still unable to provide at least one mucoid sputum sample of >1 ml will initially will be given a sputum container and asked to return it the next day. If they do not manage to produce sputum at home, their mycobacteriology results will be treated as missing. We expect ~15% of participants to fall in this category[31] and have accounted for them in the sample size estimation. For participants who produce less than the needed quantity of sputum, we will process them for the planned tests in the following priority order: 1) Xpert MTB/RIF, 2) MTB culture, 3) smear microscopy. The Xpert MTB/RIF

is the single most important guide for immediate clinical diagnosis and the MTB culture is the single most accurate reference diagnostic.

We will also collect a urine sample which we will store for subsequent lipoarabamannan antigen detection (LAM); and a nasopharyngeal swab for pneumococcal culture and sensitivity testing to estimate prevalent antimicrobial resistance. We will also perform HIV tests according to the national algorithm, and if positive we will do HIV viral load. After completing all Day-1 visit procedures, we will link the newly tested positive participants to routine HIV care and will document when they start ART (Malawi National Program provides same-Day-ART initiation to all newly-diagnosed or untreated HIV-positive patients). After the sample collections, we will collect the following information:

- Demographic data, including precise geographic locator information using ePAL geolocation software (to aid follow-up). The locator information will also include phone numbers for the participant and for up to 3 family, or friends they nominate as alternative contacts.
- Clinical history including information on tuberculosis symptoms and health care seeking for HIV and tuberculosis care services including ART, cotrimoxazole, isoniazid preventive therapy, and past TB treatment.
- Vital signs including height and weight

After completing all these baseline procedures, we will randomise the participants to the three study arms.

6.4 Assignment of interventions

Step 1: An independent statistician based at LSHTM and without contact with participants or the study staff that see participants, will use the ralloc command in Stata (StataCorp LLC, College Station, Texas USA. Release 15.0) to prepare a random allocation sequence in advance of study recruitment efforts. Randomisation will be 1:1:1 to the three arms of the trial, block-randomised with variable block sizes, and stratified by primary care centre.

Step 2: Each treatment allocation will be printed alongside a randomisation number onto a pdf document.

Step 3: The statistician will email the pdf document to an independent designee within university of Malawi who will print and place the randomisation assignments in envelopes labelled with randomisation numbers. The independent designee will hand the envelopes directly to the study pharmacist who will also receive a shipment of study medications. The pharmacist will store the envelopes in a secure location within the pharmacy.

Step 5: The pharmacist will pre-pack 625 each of protocol doses of azithromycin and amoxycillin without any reference to the allocation sequence. There is no need to refer to the allocation sequence for this step because the dosage for both treatments is the same and the total number of allocation for each treatment is known.

Step 6: At the beginning of each working week and upon request from study site, the study pharmacist will hand to site coordinators of each primary care center, a recruitment-rate-driven daily working stock of 1) the sequentially numbered sealed opaque envelopes containing randomization numbers and corresponding treatment allocations, and 2) study drugs.

Step 7: Study staff from each site will conduct patient eligibility assessments. Patients meeting the quick criteria of age and cough for ≥14 days, will be assigned screening IDs before being taken through the full eligibility criteria and consenting process. Participants will be considered eligible and ready for randomisation after they meet all criteria and sign consent.

Step 8: Upon signing consent, the participant will be taken to the site-coordinators (nurse or clinical officer) who will assign them the next available study ID number and document it on their paper and electronic eligibility checklist and enrolment CRF. The study ID number will be the number on the treatment allocation envelope plus a site-specific code. They will then open the envelope, document the treatment assignment, to the participant's enrolment paper and electronic case report forms as well as on a study card that will be pasted in the participant personal health profile book.

Step 9: The coordinator will double-check to ensure that the enrolment number and the treatment assignment are recorded correctly. They will then record screening date, screening ID, randomisation date, study ID, and randomisation arm on an enrolment log. They will then administer the allocated treatment. Administering study medications will not be considered as prescribing considering that prescription to all eligible participants will have already been done by the study protocol.

Step 10: When the stock of either envelopes or study drugs runs out,, the nurse-coordinators will reorder a from the study pharmacist.

Additional details

All steps of receipt, and utilization of the allocations and study drugs are elaborated in a detailed SOP. The SOP guides implementation of the above plan as far as possible and in line with site conditions.

The study drugs will be pre-packed blindly without any reference to treatment allocations ensuring that neither the pharmacist nor the nurse-coordinator know the treatment allocations until just before assigning to a participant.

6.5 Blinding

We will mask the treatments as far as possible. The study pharmacist will remain blinded as they will use the randomly- allocated label numbers to prepare and pack the correctly dosed study medications in opaque packaging. Study outcome assessment will occur without reference to study treatment allocation. All laboratory forms for mycobacteriology and nasopharyngeal pneumococcal work will have no reference to participant treatment allocation. On Day-8, assessment of improvement from baseline symptoms will utilize audio computer-assisted self-interview (ACASI) to minimise potential for social-mediated reporting and ascertainment biases (see Procedures Section of the protocol). All clinical endpoints assessment case report forms will bear no reference to treatment arm. However, we will keep participants, research coordinators, and routine care staff unmasked to ensure safety of the participants and allow appropriate patient management decision-making which may be related to the trial interventions.

6.6 Participant follow up

Following enrolment and completion of baseline procedures we will ask participants to return for follow up visits on days 8, and 29. They will be given 1 sputum collection bottle when leaving the clinic on Day-1 to bring with them sputum for mycobacteriology planned for Day-8 ("morning" specimen) followed by collection of one further "spot" sputum on Day-8, 2 sputum samples in total). We will also collect a second urine sample for storage for subsequent LAM antigen testing. Patients unable to produce at least one mucoid sputum sample of >1ml on Day-8 will be assumed for purposes of analysis to be mycobacterially negative for the Day-8 sputum samples. We are performing two sets of sputum examinations (Day-1 and Day-8) for each participant to strengthen the accuracy of the reference standard. Considering that TB progresses very slowly, making a diagnosis on Day-8 is not different from that made on Day-1.

We will advise participants that their sputum TB test results will start becoming available from 48 working hours after collection, but with the last test (MTB culture) taking up to 4 weeks. Patients will be advised that they will not be routinely contacted if positive TB test results become available before their Day-8 appointment (as is standard for outpatient management without danger signs in Malawi), and so will be advised to report promptly back to the clinic (with refund of transportation given) if they experience any clinical deterioration during Days 2 to 7.

In the circumstances where TB treatment is commenced before completion of antibiotics prescribed for trial-of-antibiotics (amoxicillin and azithromycin), we will ask them to carry on with their allocated intervention together with the TB treatment.

6.6.1 Day-8 activities

On Day-8, the first activity before the participants undergo all other evaluations will be documentation of self-reported improvement of baseline (Day 1) TB symptoms using a pilot-validated set of questions and answer options delivered via Audio Computer Assisted Self Interview (ACASI). We will use ACASI with the goal of eliminating inter-observer variability and patient/interviewer reporting or ascertainment biases. After a "how to use" orientation and testing session, the participant will be left alone in the room to interact with the computer. A pre-recorded interviewer will ask the participant questions related to how their symptoms have changed on that day compared to how they were on Day-1 and will offer categorised voice-recorded responses with touch screen response buttons. The ACASI questionnaire will also include questions about adherence to study arm drugs and any other medical care (including traditional medicine) sought during the previous week.

Other activities for all participants on Day-8 include:

- collection of a second sputum sample for mycobacteriology tests.
- providing participants with Day 1 smear and Xpert results linking those with positive tests, ongoing symptoms and other illnesses with routine care for appropriate management.
- clinical history detailing clinical events since enrolment.
- documentation of any medications including antimicrobials and traditional medicine outside the study
- providing a study Day-29 appointment card

For participants with negative Day-1 mycobacteriology results we will perform clinical evaluation after ACASI and will inform the patient that any positive Day-8 sputum mycobacteriology results will be reported actively (via telephone or house visit) as soon as quality-assured results become available (within 48 working hours for microscopy and Xpert). Patients who have not had complete resolution of symptoms will be referred with all available results to routine primary care management.

6.6.2 Day-29 activities

Day-29 will be the final study visit. We will on this visit, collect data on clinical impact of antibiotic treatment and risk of AMR. In line with the second primary endpoint (composite clinical impact), we will document:

1) vital status
2) hospitalisations
3) identify missed TB diagnosis by using culture results from Day 1 and Day 8 sputum, any chest X-rays performed in follow up, and repeat mycobacteriology if symptomatic
4) perform HIV tests for those with unknown status and eligible for routine HIV test.

We will first collect information on clinical events prior to and at the visit and communicate all available sputum culture results and the final reported CXR results.

After collecting the clinical information, we will collect nasopharyngeal swab sample for assessing antimicrobial resistance. To collect the sample, a trained study staff will swab the participants' nasopharynx and place the swab in a tube containing skim milk tryptone glucose glycerol (STGG).

6.7 Laboratory methods

6.7.1 Tuberculosis mycobacteriology

We will process mycobacteriology tests at the Malawi College of Medicine TB laboratory, a reference laboratory located in Blantyre. For sputum samples collected on Day-1, we will perform smear microscopy, Xpert MTB/RIF and MTB culture. For sputum samples collected on Day-8, we will perform smear microscopy and MTB culture. We will use Mycobacteria Growth Indicator Tube (MGIT) and Lowenstein-Jensen (LJ) culture methods for TB culture. Once isolated, we will perform speciation as *Mycobacteria tuberculosis* (MTB) or non-tuberculous mycobacteria (NTM) using MBP84 antigen testing, microscopic cording and, if necessary, morphology and growth characteristics at different temperatures and on solid (LJ) media containing p-nitrobenzoic acid (PNB).

6.7.2 Urine antigen testing for lipoarabamannan and other MTB antigens

Urine will be collected and stored as two 1 ml aliquots at -20°C from each participant on both Day-1 and Day-8 for subsequent mycobacterial antigen testing. No appropriate product is available for immediate use, but we anticipate that a commercial product with sufficiently high analytic accuracy for use in ambulant outpatients (sensitivity and specificity) may become available during the course of, or soon after, the study. If ongoing evaluations of the FIND-sponsored FujiFilm product[45] meet or exceed pre-specified requirements for clinical utility in the outpatient context, then point-of-care LAM testing at Day-1 and Day-8 will be added to the mycobacteriological definition of TB and patient management as soon as kits have been obtained and evaluated in Malawi.

6.7.3 Antimicrobial resistance testing

We will store swabs in STGG at minus 80°C. At a later stage we will thaw them in batches, and plate them onto selective media and culture colonies consistent with *S. pneumoniae*. We will determine

Minimal inhibitory concentrations (MICs) using E-test strips (azithromycin and amoxicillin), and Kirby Bauer Disc diffusion testing (azithromycin, rifampicin, tetracycline, ceftriaxone, chloramphenicol, co-trimoxazole, erythromycin and penicillin) and define resistance by EUCAST breakpoints.

We will store isolates and remaining STGG at minus 80°C to allow genotypic characterization, isolation and susceptibility testing of other key respiratory pathogens, FTD 33 respiratory pathogen diagnostic panel, metagenomics analysis, and microarrays to detect multiple carriage and macrolide resistance genes in a broader range of pathogens at a later stage.

6.8 Loss to follow-up

To minimise loss to follow up, we will at enrolment record geolocation information of participants' place of residence using ePAL android app, a high-resolution mapping system validated in Blantyre. We will also record up to 3 contact phone numbers of the participant and their nominated friends and relatives. Should a participant miss a study visit, we will contact them by phone or by visiting them at home to encourage them to attend the study visit before expiry of prescribed visit window.

We anticipate a loss to follow-up of 5% by Day-8, and 10% by Day-29. We have accounted for these assumptions in the sample size calculation. We will not replace participants who discontinue study participation or study treatment regardless of reason for withdrawal or discontinuation or the time either of these occurs.

6.9 Trial closure

We will consider the trial closed after completing follow up of the last enrolled participant, and upon recording all mycobacteriology laboratory reports. Antimicrobial resistance lab work will continue beyond trial closure. The trial may be terminated early by the trial steering committee upon recommendation of the DSMB. The halting rule for a trial arm is an unacceptable high level of deaths assessed using an alpha determined at the first DSMB meeting.

6.10 Summary schedule for study procedures

In Table 5 below, we have summarised all key study procedures over the study period.

Table 5: key study procedures over the study period

	STUDY PERIOD			
	Enrolment	Follow up		
TIMEPOINT**	**Day-1**	***Day-8***		***Day-29***
ENROLMENT:				
Eligibility screen	X			
Informed consent	x			
Allocation	x			
INTERVENTIONS:				
Azithromycin	x			
Amoxicillin	x			
Standard of care	x			
ASSESSMENTS:				
Demographics	x			
History of antibiotic use	x	x		x
**History & examination*	x	x		x
***Sputum collection*	x	x		
Urine for TB LAM test	x	x		
Nasopharyngeal swab	x			x
HIV test and CD4 count	x			x
Linking to routine care	x	x		x
[1]*ACASI*		x		
***Clinical events*		x		x
Update contact & address		x		x

*For symptomatic participants, Day-8 sputum mycobacteriology should be fast-tracked to inform care before they leave the clinic. Chest X-ray should be performed and interpreted in real-time.

**Give sputum bottles at end of Day-1 visit for submission on Day-8. Also collect sputum and perform mycobacteriology at any time of the study when clinically indicated

***Illnesses, clinic visits, radiological outcomes, new HIV diagnosis, new TB diagnosis, death, hospitalisation, missed TB diagnosis, HIV care loss to follow up, and TB care loss to follow up

[1]Audio Computer Assisted Self-Interview for documenting change of symptoms on Day- 8 versus Day-1

7 Safety reporting

7.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product.

7.2 DMID grading for AEs

We will adopt the events grading criteria prepared by the Division of Microbiology and Infectious Diseases (DMID) of the USA National Institutes of Health as shown in the table below.

1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
Transient or mild discomfort (< 48 hours); no medical intervention required	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention required	Marked limitation in activity, some assistance usually required; medical intervention required, hospitalizations possible	Extreme limitation in activity, significant assistance required; significant medical intervention required, hospitalization probable

7.3 Grading for expected events

The following table provides guidance for grading known important or frequent side effects of azithromycin (based on the AE grading criteria provided in the BREATHE Trial Protocol, also investigating azithromycin) and amoxicillin graded on the DMID scale. All events not mentioned here or in Appendix 2, will be graded using the DMID grading for AEs table presented above.

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
Side-effects	**1**	**2**	**3**	**4**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal oedema
Rash ***Specify type, if applicable***	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Mental state changes	mild anxiety or depression	moderate anxiety or depression; therapy required;	severe mood changes requiring therapy; or suicidal ideation;	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
		change in normal routine	or aggressive ideation	
Photosensitivity	Painless erythema covering <10% body surface area	Tender Erythema covering 10 - 30% body surface area	Erythema covering >30% body surface area and erythema with blistering, requiring intervention	Life-threatening consequences; urgent intervention indicated
Arrhythmia (by ECG or physical examination) ***Specify type, if applicable***	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Prolonged QTc Interval	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Nausea	Transient (< 24 hours) or intermittent AND No or minimal	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration	Life-threatening consequences (e.g., hypotensive shock)

	1 MILD	2 MODERATE	3 SEVERE	4 LIFE-THREATENING
	interference with oral intake		indicated (e.g., IV fluids)	
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Laboratory	**1**	**2**	**3**	**4**
ALT or SGPT, High ***Report only one***	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Creatinine Clearance or eGFR, Low ***Report only one***	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed

7.4 Causality

When reporting on serious adverse events, the trial investigator will state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship. They will also state whether the adverse event was expected and what if any action was taken.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.5 Reporting Procedures

7.5.1 Non-serious Adverse Events (AEs)

Adverse events will be ascertained from patient follow-up visits or reports from relatives or guardian if patient cannot be contacted for follow-up. Study clinicians will be responsible for recording of details of the event including a description of the event, date of onset, severity, assessment of relatedness to trial interventions. Adverse events will be recorded in case report forms and uploaded into the study database.

7.5.2 Serious Adverse Events (SAEs*)*

All serious adverse events (SAEs) will be recorded on the relevant study CRFs and reported immediately to the Principal Investigator who will ensure that they are compiled in aggregate form and reported to COMREC and the DSMB once every 6 months. The DSMB will review SAE reports at their 6 monthly meetings and issue recommendations which will be shared with ethics committees. Events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition will not be reported as SAEs.

8 Economic evaluation

8.1 Objective

The objective of the economic evaluation is to undertake a cost-utility analysis to estimate the incremental cost-effectiveness of trial-of-antibiotics using azithromycin and trial-of-antibiotics using amoxicillin in comparison to standard of care, and to each other. We will systematically compare costs and consequences associated with the interventions.

8.2 Outcomes

We will perform a within trial comparison of the three treatment arms to estimate the incremental cost per quality-adjusted life year (QALY) gained for the azithromycin or amoxicillin arm in comparison to standard of care. Costs will be estimated from the Malawian Ministry of Health perspective. Health outcomes will be quantified in QALYs, estimated from participants' responses to the Chichewa version of the EQ-5D-3L, a Health quality of life (HRQoL) measure.[46,47] We will adopt a time horizon matching the length of participant follow-up to achieve the within trial evaluation.

8.3 Data collection

The health economic data collection will be undertaken alongside planned clinical data collections. We will administer the Chichewa version of the EQ-5D-3L to all trial participants at baseline (Day1), Day 8 and Day 29. The Chichewa EQ-5D-3L was prepared in accordance with international and EuroQoL guidelines. The EQ-5D uses a descriptive system and a visual analogue scale (VAS). HRQoL on the day of response is defined using the descriptive system in terms of the following dimensions: 1) mobility, 2)self care, 3)usual activities, 4)pain/discomfort, and 5) anxiety or depression. The responses are then split into the following ordinal levels: 1) no problems; 2) some or moderate problems; and 3) severe or extreme problems.

The EQ-5D has 243 health states to which each response is allocated and converted to an EQ-5D utility score using a tariff. Tariff sets are derived from national surveys and currently no Malawian EQ-5D tariff exists. Zimbabwe, a setting similar to Malawi, has EQ-5D tariff set. In this study, we will use the Zimbabwean set to derive EQ-5D utility scores[48] an acceptable practice considering the similarities in how the two populations value health.[49] The EQ-5D utility scores in the Zimbabwean tariff, range from 1.0 (which means no problems in the five dimensions) to -0·29 (defined as severe problems in all five dimension).

We will capture all healthcare resources used by trial participants from recruitment into the trial till Day 29. This will be undertaken on Day 1, Day 8 and Day 29. Healthcare resources will be translated into direct medical costs using previously estimated costs[47,50,51] and the wider literature.

Drug prices will be based on International market prices.[52] The health resource use questionnaire will at a minimum capture:

- Outpatient clinic visits
- Days of inpatient hospital care
- Medications
- Investigations and procedures

8.4 Data analysis

Our primary analysis will focus on direct intervention and the broader healthcare costs. We will define direct intervention costs as the costs associated with the application of the interventions. We will plot health state values measured by the EQ-5D-3L against time assuming that the health states reported at each time point are linearly connected. We will estimate QALYs associated with participant health profile by area under the plotted curve as calculated using the trapezium rule.

We will use a range of analytical methods depending on whether baseline covariates (EQ-5D utility values) are balanced between the trial arms or not. If they are balanced, we can obtain unbiased cost-effectiveness estimates by using non-parametric bootstrap approaches; if imbalance exists regression methods will be the approach of choice.

We will explore a range of estimators and undertake model diagnostics to determine the optimal model because the distributions of costs and QALYs are commonly skewed, often bimodal, or truncated. We will estimate mean costs and outcomes for each intervention together with respective mean incremental cost-effectiveness ratio. We will for each estimate report respective measures of uncertainty (standard errors and confidence intervals). We will also estimate the net monetary benefits (NMBs) for a range of different willingness to pay (WTP) thresholds. To identify the optimal intervention at different WTP thresholds, we will construct cost-effectiveness acceptability curves (CEACs) based on the NMB framework.

8.5 Missing data

For each participant we will collect complete data as far as possible but in cases of missing values, a common occurrence in trials, we will perform additional analyses to explore the impact of and account for the missingness.

9 Data management

9.1 Source Data

We will consider a document as source if it is where data were first recorded, and from which we obtained participants' case report forms (CRF) data. These will include hospital records, health center records, participant health passport, laboratory and pharmacy records, diaries, radiographs, and correspondence. We will consider CRF entries as source data if the CRF is the site of the original recording.

We will on all study-specific documents, other than study ID code list, the signed consent forms household locator form and, refer to the participant by their trial participant identification number, not by name. We will keep study ID code list, consent and locator forms separate from the rest of the participant file to avoid linkage between participant name and the study ID.

9.2 Data collection methods

We will collect data using standardised, pre-tested CRFs in two forms:

- programmed into android tablets using Open Data Kit (ODK) platform (opendatakit.org) with paper back-ups.
- optical mark recognition readable forms read and extracted using TELEFORM system (Cardiff Software, Inc., Vista, CA), an optical-character-recognition software.

9.3 Data management

Any participants' identifiable data collected by the Study Coordination Centre will be stored securely and their confidentiality protected in accordance with the Data Protection Act 1998.

To ensure data security and maintenance of participant confidentiality, we will take several strict measures. All the study data collection tablets and computers will be encrypted, password protected and stored in a fireproof lockable cabinet inside a locked room. The principal investigator, study coordinator and data manager will be responsible for the maintenance of the tablets as well as all other computers, and their security from viruses and theft. All users will check in with the study coordinator and sign for data entry tablets every time they are taken out to for data entry and upon return. Whenever not in use, the devices will be kept in their locked cabinet.

We will keep all paper records in a locked space only be accessible to the principal investigator, co-investigators and delegated study staff. Study databases will be encrypted, password protected and will be stored on dedicated servers within the University of Malawi College of Medicine. We will keep all electronic and paper records securely for up to 10 years after the end of the trial in accordance with LSHTM Records Retention & Disposal Schedule guidelines.

9.4 Quality control and quality assurance

We will apply quality control at each stage of data handling in accordance with GCP requirements to ensure that all data are reliable and have been processed correctly. We will manual review all paper CRFs for completeness, accuracy and legibility before scanning. Our ODK data entry system will include automatic pre-programmed real-time data validation. The TELEFORM system will also have pre-programmed automatic data validation capabilities. We will perform data quality assurance (QA) on a random 10% of all participant files. The QA process will involve examining database entries and for paper source documents, verification of database entries and source.

9.5 Access to data

We will upon request, provide direct access to authorised representatives from the Sponsor, host institution and the regulatory authorities to allow smooth running of trial-related monitoring, audits and inspections.

10 Data monitoring and quality assurance

10.1 Data monitoring

Site monitoring for safety will be conducted to ensure human subject protection. The study will be monitored just before commencing enrolment, then once every 6 months by a monitoring team from the University of Malawi College of Medicine. The objective will be to ensure that study procedures, study products administration, and data collection processes are of high quality and meet ethical and regulatory guidelines. The regular monitoring will focus on the following areas: 1) protocol adherence, 2) informed consent documentation, 3) trial endpoints, 4) treatment discontinuation, 5) regulatory documents, 6) compare source documents and case report forms for accuracy, and 7) documentation practices in general.

10.2 Audits and Inspections

The study will be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

10.3 Data Safety and Monitoring Board (DSMB)

We will set up a DSMB before commencing trial activities. The DSMB will provide independent review of the study conduct, progress and findings. It will comprise 3 members including a chairperson who will be responsible for collating and communicating the views of the DSMB. The DSMB will consist of an independent statistician and two clinicians, at least one of them a physician, with research experience and expertise in the management of tuberculosis and HIV in Africa. The proposed data safety monitoring plan will be discussed in a teleconference including the DSMB members and the key investigators prior to the study starting.

The proposed meeting schedule is 6 monthly. Two weeks before a 6 monthly DSMB meeting, the study team will prepare a report covering study progress, study approvals, any obstacles, and recruitment statistics, adverse events, withdrawals and trial outcome measures. The DSMB will, through its chairperson, provide written feedback to the principal investigator who will be responsible for passing it on to ethics committees.

10.4 Trial Management Group (TMG)

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-Day-management of the trial will be co-ordinated through the University of Malawi College of Medicine.

10.5 Trial Investigational Team

Our investigational team includes expertise in diagnosis and management of TB; clinical evaluation of TB diagnostics; design and conduct of large randomised controlled trials; laboratory TB and AMR diagnostics; data management and analysis.

Chief investigator

Dr Titus H Divala: the chief investigator and PhD student will be responsible for protocol development, coordination and conduct of the trial, governance, data management, data analysis and results dissemination. Dr Divala is a clinician with a career interest in clinical trials. Apart from medical training, he holds MPH and Masters of Science in epidemiology and preventive medicine. He has managed two large GCP, US-NIH-funded clinical trials, one of which was IND as the local PI supervising over 40 study staff at two sites in different cities. He has worked as a clinician for over 8 years in Malawi, a period when identifying TB cases and putting them on treatment was a daily job. This topic therefore falls in area of great personal interest above and beyond the potential benefit it has towards improving patient care in Malawi and all low and middle-income countries where 95% of the TB burden lies, where this approach is the standard.

Co-investigators and members of PhD supervisory team

Prof Katherine L Fielding: a seasoned TB statistician and clinical trialist, and PhD supervisor for the CI, will be responsible for protocol development, conduct of the study, and data dissemination.

Prof Elizabeth L Corbett: a seasoned TB clinical epidemiologist and PhD co-supervisor for the CI, will be responsible for protocol development, conduct of the study, and data dissemination.

Co-investigators and members of PhD advisory committee

Dr Derek J Sloan: clinician with detailed local clinical and research experience, will be responsible for protocol development, trial implementation and data dissemination.

Prof Neil French: a seasoned pneumococcal expert, will be responsible for protocol development, oversee all aspects of AMR work, and data dissemination.

Collaborators

Dr Marriott Nliwasa: clinician, with experience conducting studies in the study setting. He will be support the conduct of the study, linkage with the national program, and data dissemination.

Mr Augustine Choko: statistician, with expertise and experience in using ACASI. He will support ACASI development, data management and development of analysis plan.

Dr Ankur Gupta-Wright: clinician, will provide clinical input in protocol development and clinical consultation support to research coordinators during study implementation..

Dr Jennifer Cornick: microbiologist, will be support protocol development, and AMR laboratory methods and analysis, and data dissemination.

Prof Jon Øyvind Odland: Epidemiologist and honorary professor at University of Malawi College of Medicine, responsible for seeking ethical approvals from the funder appointed ethics committee.

11 Ethics and dissemination

We will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki and in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6 (R2) of November 2016.

11.1 Risk assessment

This is a low risk study as it is using already licensed antibiotics with good safety profile in a population defined by national clinical guidelines as clinically stable and not requiring other intervention but TB investigations. Our work complements standard of care by bringing in detailed TB diagnostics. In our study, the standard of care equivalent of the antibiotics we will prescribed on Day-1 to those randomised to either azithromycin or amoxicillin arms, are in standard of care prescribed on Day-8 only to mycobacteriology negative symptomatic patients (similar to the no antibiotic or standard of care arm of our trial). So, participants randomised to no antibiotic at Day-1 will not be receiving inadequate care but the recommended standard management of withholding antibiotics until after the TB results are available (Figure 1). To maintain participant safety and continuity of their care while on study interventions, we will not blind routine care clinical team and they will be free to manage the participants on their clinical judgement and national guidelines.

11.2 Research ethics approval

We will seek ethical approval for the trial protocol, informed consent forms, participant information sheet, any advertising material, and amendments to any of these documents, from the University of Malawi College of Medicine Research and Ethics Committee (COMREC), the LSHTM Research Ethics Committee, and Regional Committee for Health and Research Ethics, NTNU-Midt, Norway (on behalf of the funder). We will seek regulatory approval from the Malawi Pharmacy, Medicines, and Poisons Board (PMPB). Every year when the trial is active, we will seek continuous ethical review and approval before expiry of previous year's approval. In the event of an amendment, the changes will only be implemented upon ethical and regulatory approval.

11.3 Indemnity

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.4 Sponsor

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.5 Declaration of interests

The study team declares that they have no conflict of interest in conducting this clinical trial.

11.6 Cost of participation, ancillary and post-trial care

During the study, participant will benefit from frequent interaction with clinical study staff and associated optimised management of illnesses. There are minimal risks including discomfort associated with collection of nasopharygeal samples, and side-effects of study interventions. We will reimburse participant transport for attending study visits.

11.7 Dissemination policy

This work will form part of a PhD thesis for Titus Divala, which he will submit to the London School of Hygiene & Tropical Medicine (LSHTM). All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator.

Members of the TMG and the DSMB will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy

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13 Appendix 1: Informed consent

Included as a separate document on headed pages.

14 Appendix 2: Division of Microbiology and Infectious Diseases (DMID) adult toxicity table

TABLE VERSION: November 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal LLN = Lower Limit of Normal R_x = Therapy Req = Required

Mod = Moderate IV = Intravenous ADL = Activities of Daily Living Dec = Decreased

- **ESTIMATING SEVERITY GRADE**

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 Mild Transient or mild discomfort

(< 48 hours); no medical intervention/therapy required

GRADE 2 Moderate Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 Severe Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 Life-threatening Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THIS TABLE

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide for Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/d L	8.0 - 9.4gm/dL	6.5 - 7.9 gm/d L	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/ mm^3	750-999/ mm^3	500-749/ mm^3	<500/ mm^3
Platelets	75,000-99,999/ mm^3	50,000-74,999/ mm^3	20,000-49,999/ mm^3	<20,000/ mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 / mm^3	15,000-30,000/ mm^3	>30,000 or <1,000 / mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ ml	41-50 mcg/ ml	51-60 mcg/ ml	> 60 mcg/ ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/l	> 7.0 mEq/ L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/d L or abnormal glucose *with* mental

				status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/d L or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/d L	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/d L	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN

increase in other liver function test)				
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/d L	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
EN ZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day

Hematuria	microscopic only \<10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion
CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment

Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused
RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy
GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4

Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/Day-or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/Day-or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink flu ids; requires IV fluids
NEUROLOGICAL				

	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at	sensory loss involves limbs and trunk; paralysis; or seizures

	focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	ankles) and/or joint position or mild impairment that is not symmetrical	least mod degree in multiple different body areas (i.e., upper and lower e xtremities)	
MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no	muscle	severe muscle	frank

	limitation of activity	tenderness (at other than injection site) or with moderate impairment of activity	tenderness with marked impairment of activity	myonecrosis
SKIN				
	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	

Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

15 Appendix 3: Package insert for Azithromycin and amoxicillin

Included as separate attachments.

PARTICIPANT INFORMATION SHEET

Participant information sheet

What is the benefit and unintended consequences of using antibiotic treatment as a way of excluding tuberculosis disease in patients with cough?

Introduction

We would like to invite you to take part in a research study. Joining the study is entirely up to you. Before you decide, you need to understand why the research is being done and what it would involve. One of our team will go through this information sheet with you, and answer any questions you may have. Ask questions if anything you read is not clear or you would like more information. Please feel free to talk to others about the study if you wish. Take time to decide whether or not to take part.

What is the purpose of the study?

Tuberculosis (TB) is a disease that causes a long illness and cough with sputum. Although curable TB is difficult to detect. When they fail to detect TB after testing sputum, clinicians give antibiotic treatment that can cure all other causes of TB symptoms but not TB. In this approach, TB is considered ruled out if patient gets better and it is considered likely if they do not get better. The goal of this research study is to develop understanding of how well the antibiotics help distinguish TB patients from those who do not have it, whether giving antibiotics carries other health benefits, and whether it leads to development of disease causing organisms which are resistant to drugs.

We will learn about this by comparing a group of patients given antibiotics on the first day of the study to another group not given antibiotics. There will be two groups receiving antibiotics as follows: 1) Azithromycin taken as one tablet once a day for 3 days, and 2) Amoxicillin 4 capsules taken three times a day for 5 days. The group you will go into, out of the three, will be decided by chance so you can fall into any group.

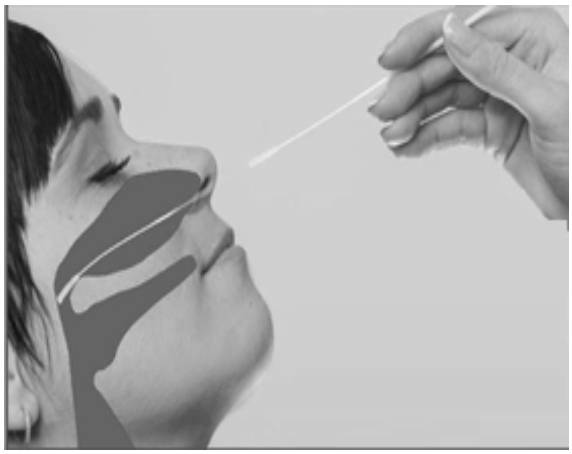
What will be involved if I accept to participate in the study?

We are considering you for participation in this study because you told us that you have a cough. Any patient who has been coughing for at least 2 weeks, is at least 18 years, and lives within Blantyre, is eligible to participate in this study if they do not have signs consistent with serious illness. Apart from you, we will recruit 1,874 other individuals.

Study activities will be performed the first day, at 1 week (Day 8), and at one month (Day 29). At each of these study visits, we will ask you questions about your contact details, your health, use of medications, and any illnesses or hospitalisations you may have had in between study visits. We will also document relevant details from your health passport and other clinical documentation you may have.

On Day 1 and at 1 week, we will ask you to submit sputum and urine samples for TB tests. If you are not able to give sputum on Day 1, we will give you containers so that you can bring them the following morning. Some of the sputum TB tests results will become available after 7 days and we will pass them to health center clinicians who will make a plan for your care, the other results may take up to 4 weeks so you will get them at the 1 month visit. Urine TB test results will not be available for your clinical care.

We will also do an HIV test. If the results are confirmed to be HIV positive we will do a viral load test, and at the end of the study activities on Day 1, we will link you to HIV management team here at the health center who will start you on treatment. Should we make a diagnosis of TB or HIV at any other point during the study, we will link you with the responsible health center team for treatment services.



On day 1 and at 1-month visit, we will swab the back of the inside of your nose as shown in this picture to collect germs that live there. We will test the germs for drug resistance. Results of this test are not relevant to your care.

On 1-week visit, we will ask you to report how your health has changed in comparison to how you were on day 1. These questions will be read to you by a computer and you will answer them by choosing various options which it will display during the interview.

The 1 month visit will be the final study visit where we will also provide you with results for TB culture and ask if you have TB symptoms. If you are in HIV or TB care, we will ask how your follow up is going. The appointment with you at 1 months is very important because it will help you to know the results of the TB tests and it will also help us know the status of your health.

The number of clinic visits you will make for this study is at least three. Here we count Day 1, one visit after one week, and another visit at one month. If you have not been able to come here for any of the visits, we will remind you by phone call or we will use the permission and information you will give us to visit you at your home. The first visit will take about 60 minutes and the later visits will take about 30 minutes each.

Will there be any risks involved in this study?

This study is a low risk study. There are no risks involved in submitting sputum or urine for the study. You may feel some discomfort during swabbing of the back of the nose and during blood collection for HIV and viral load tests. Azithromycin and amoxicillin are already widely used in Malawi and rarely cause problems. Rare side effects for azithromycin include feeling nervousness, skin reactions and disturbance of heart function. Rare side-effects for amoxicillin are mental state changes, feeling light-headed, and reactions to sunlight.

The London School of Hygiene and Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation.

Will there be any benefits in this study?

The key benefit of this study is that you will have access to a more detailed TB evaluation process than usual. This will help you know if you have TB and to have the opportunity to start TB treatment. The study is also beneficial to health care providers because it will address important questions about use of antibiotics during the TB diagnostic process.

Will the findings in the study be confidential?

Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you. Information about TB test result and HIV test results will be recorded using an identification number. However, any records or data obtained as a result of your participation in this study may be used by LSHTM who are sponsoring this study, regulators of health research (COMREC), or by members of the research team. These records will be kept in a locked space in the University of Malawi College of Medicine. Information and samples collected in this study will be retained for up to 10 years after the end of the trial, according to our institution recommendations. These collected samples and other information may also be used for future studies if you give us that consent.

Can I withdraw from the study anytime and will this affect my treatment?

You are free to choose whether or not to participate in this study. While we would like you to participate in the study to the very end, withdrawing at any point is an option that is freely available to you without any penalty or loss of any entitled benefits. You will be provided with any significant new findings developed during the course of this study that may relate to or influence your willingness to continue participation.

What are the financial benefits of participating in this study?

There will be no payment given to you for participating in the study. The study will provide at least MK8,000 as compensation for your costs of attending the study visits. We will give this money in instalments on scheduled study visits.

Is this study approved by an ethics committee?

The study has been approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee, and the College of Medicine Research Ethics Committee (COMREC).

Who do you ask if you have questions regarding the study?

If you have any questions concerning participation in this study, please feel free to ask me. Alternatively, you can contact the following people by phone or post:

	Name	Telephone	Postal address
Study investigators	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi
	Dr Marriott Nliwasa	0888681948	
COMREC			
	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

What is the benefit and unintended consequences of using antibiotics treatments as a way of excluding tuberculosis disease in patients with cough?

Patient declaration

Statement	Initial or thumbprint each box
I confirm that I have read the above information sheet for the above named study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. OR I have had the information explained to by study personnel in a language that I understand. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from LSHTM, University of Malawi College of Medicine, and COMREC, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that data about me may be shared via a public data repository or by sharing directly with other researchers, and that I will not be identifiable from this information	
I understand that the tissue sample collected from me will be used to support other research in the future, and may be shared anonymously with other researchers, for their ethically-approved projects	
I agree to take part in the above named study	

Printed name of participant	**Signature/thumb print of participant**	**Date**
Printed name of impartial witness*	**Signature of impartial witness***	**Date**

I attest that I have explained the study information accurately to _____, and was understood to the best of my knowledge by, the participant and that he/she has freely given their consent to participate* in the presence of the above named impartial witness (where applicable).

Printed name of staff obtaining consent	**Signature of staff obtaining consent**	**Date**

*Impartial witness should be someone the participant trusts. The impartial witness can write the participant name but cannot sign for them. Instead, illiterate participants should use thumbprint in place of signature and the impartial witness should go ahead and sign in designated space.

A copy of this informed consent document to be offered to the participant

Study title: Randomised controlled clinical trial of diagnostic value, clinical benefits and unintended consequences of using trial-of-antibiotics to evaluate ambulatory adults with prolonged cough for tuberculosis in Malawi

Version & Date: 3.0/28 Feb2019

Principal Investigator: Dr Titus H Divala REC ref: LSHTM 15232; COMREC P.04/18/2381

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PARTICIPANT INFORMATION SHEET

Chikalata chofotokozera ofuna kutenga nawo mbali

Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufifuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

Chiyambi

Tikukukupemphani kuti mutenge nawo mbali mu kafukufuku. Ndi chifuniro chanu kulowa mu kafukufukuyu. Musanapange chiganizo, mukuyenera kumvetsa chifukwa chimene kafukufukuyu akuchitikira komanso zimene zitadzachitike. M'modzi mwa anthu a gulu logwira ntchito mu kafukufuku awerenga chikalatachi pamodzi ndi inu, ndipo ayankha mafunso ena aliwonse amene mungakhale nawo. Funsani mafunso ngati simukumvetsa zomwe mwawerenga kapena ngati mukufuna uthenga owonjezera. Muli omasuka kulankhula ndi ena zokhudza kafukufukuyu ngati mukufuna. Ganizani mofatsa musanavomereze kutenga nawo mbali kapena ayi.

Kodi cholinga cha kafukufukuyu ndi chiyani?

Chifuwa chachikulu (TB) ndi matenda amene munthu amkhala chidwalire kwa nthawi yaitali. Odwalayo, amapanga makhololo. Ngakhale chili chochizika, chifuwa chachikulu ndi chovuta kuchipeza. Pamene njira zoyeza makholoro zalephera kupeza chifuwa chachikulu, achipatala amapereka mankhwala opha tizirombo toyambitsa matenda amene angathane ndi zonse zimene zimayambitsa zizindikiro za matenda ofanana ndi chifuwa chachikulu. Ngati odwala apeza bwino ndi njira imeneyi amaganiziridwa kuti alibe matenda a chifuwa chachikulu koma ngati sanapeze bwino amaganiziridwa kuti ali ndi chifuwa chachikulu. Cholinga cha kafukufuku ameneyu ndi kufuna kumvetsa za m'mene mankhwala amenewa amathandizira kusiyanitsa odwala matenda a chifuwa chachikulu ndi amene alibe matendawa, ngati mankhwalawa ali ndi phindu lina kwa odwala, komanso ngati kupereka mankhwalawa kukubweretsa tizirombo tosamva makhwala.

Tiphunzira zimenezi pakusiyanitsa gulu la anthu odwala amene apatsidwa mankhwala opha tizirombo toyambitsa matenda patsiku loyamba la kafukufukuyu ndi gulu lina limene silinapatsidwe mankhwalawa. Pakhala magulu awiri olandira mankhwala opha tizirombo motere: 1) Azitrhomycin omwedwa pilisi imodzi kamodzi patsiku kwa masiku atatu, komanso 2) Amoxicillin makapusolo anayi omwedwa katatu patsiku kwa masiku asanu. Gulu limene mulowe, mwa magulu atatuwa, lisankhidwa mwa mayere choncho mukhoza kupezeka mu gulu lina lirilonse.

Kodi chidzachitike ndi chiyani ngati ndingavomereze kutenga nawo mbali mu kafukufukuyu?

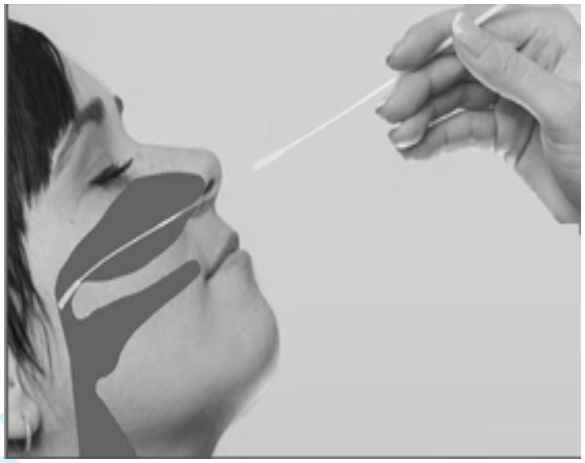
Tikukupemphani kuti mutenge nawo mbali mu kafukufukuyu chifukwa mwatiuza kuti muli ndi chifuwa. Odwala wina aliyense amene wakhala akukhosomola kwa masabata osachepera awiri, ali ndi zaka zosachepera 18, ndipo amakhala mu Blantyre muno, atha kutenga nawo mbali mu kafukufukuyu ngati alibe zizindikiro zosonyeza kudwalika kwambiri. Kupatula inu, tilemba anthu ena okwanira 1,874.

Zochitika za kafukufukuyu zidzapangidwa patsiku loyamba, pa sabata imodzi (Tsiku 8), ndi pamwezi umodzi (Tsiku 29). Pa masiku a kafukufuku onsewa, tidzakufunsani mafunso okhudzana ndi m'mene tingalumikizirane nanu, thanzi lanu, kagwiritsidwe ntchito ka mankhwala, ndi matenda ena aliwonse kapena kugonekedwa mu chipatala komwe kungakuchitikireni. Tidzalembanso zinthu zofunikira

kuchokera mu bukhu lanu la kuchipatala komanso zolembedwa zina za chipatala zimene mungakhale nazo.

Patsiku loyamba ndi pakutha pasabata yoyamba, tidzakufunsani kuti mupereke makhololo komanso mkodzo pofuna kuyeza matenda a chifuwa chachikulu. Ngati simungakwanitse kupereka makhololo patsiku loyamba, tidzakupatsani mabotolo kuti mudzawabweretse m'mawa wa tsiku lotsatira. Zotsatira zina za makhololo zidzatuluka pakutha pa masiku asanu ndi awiri ndipo tidzazipereka kwa matodolo a chipatala chino kuti akuthandizeni, zotsatira zina zidzatenga pafupi-fupi masabata anayi choncho mudzazilandira pa ulendo wa pamwezi umodzi. Zotsatira zanu zoyesa mikodzo ku matenda a chifuwa chachikulu sizidzakhalapo ku nkhani ya chisamaliro chanu cha kuchipatala.

Tidzayezanso kachirombo ka HIV. Ngati zotsatirazi zasonyeza kuti muli ndi kachirombo ka HIV tidzayeza kuchuluka kwa tizirombo ta HIV, komanso kukutumizani kolandilira chithandizo chamatendawa. Ngati tingakupezeni kuti muli ndi matenda a chifuwa chachikulu kapena kachirombo ka HIV panthawi ina iliyonse mkati mwa kafukufukuyu, tidzakutumizani kolandilira zithandizo zamatendawa pompano pachipatala.



Patsiku loyamba komanso pa ulendo wa mwezi woyamba, tidzapukuta kumbuyo kwa mkati mwa mphuno mwanu ngati m'mene zikuonekera pachithunzichi kuti titenge tizirombo timene timakhala m'menemo. Tidzayeza tizirombo timeneti kuti tione ngati tikumva mankhwala. Zotsatira zimenezi sizidzagwiritsidwa ntchito kuchisamaliro chanu chaku chipatala.

Pa ulendo wa sabata yoyamba, tidzakupemphani kuti mutiuze m'mene thanzi lanu lasinthira kuyerekeza ndi m'mene munaliri patsiku loyamba. Mafunso amenewa adzawerengedwa kwa inu kudzera pa makina a kompyuta ndipo mudzawayankha pakusankha mayankho angapo amene makinawa adzawonetse panthawi yomwe azidzafunsa.

Ulendo wa pa mwezi umodzi udzakhala wotsiriza umene tidzakupatseninso zotsatira za zoyesa za matenda a chifuwa chachikulu komanso tidzakufunsani ngati muli ndi zizindikiro za matenda a chifuwa chachikulu. Ngati panthawiyi mudzakhale kuti mukulandira Thandizo la HIV kapena TB, tidzakufuna kudziwa kuti zikuyenda bwanji. Kukumana ndi inu patatha mwezi umodzi ndikofunikira kwambiri chifukwa zidzakuthandizirani kuti mudziwe zotsatira za zoyeza za matenda a chifuwa chachikulu ndipo zidzatithandiziranso kudziwa zam'mene thanzi lanu liliri.

Maulendo a kuchipatala amene mudzayende a kafukufukuyu ndiwosachepera atatu. Pamenepa tikuwerenga tsiku loyamba, ulendo umodzi pakutha pa sabata imodzi, ndi ulendo umodzi pa mwezi umodzi. Ngati simunakwanitse kubwera kuno pa ulendo wina uliwonse tidzakukumbutsani pokuyimbirani lamya kapena tidzagwiritsa ntchito chilorezo ndi uthenga umene mudzatipatse kuti tikuyendereni kunyumba kwanu. Patsiku loyamba tidzakhala nanu kwa mphindi makumi asanu ndi imodzi, pamene paasiku ena onse, tidzakhala nanu kwa mphindi makumi atatu.

Kodi padzakhala ziopsezo zina zilizonse zochitika mu kafukufukuyu?

Kupanga nawo kafukufukuyu sikuika moyo wanu pa chiopsyezo chochuluka. Palibe chiopsezo pa kupereka makhololo kapena mikozo mu kafukufukuyu. Mukhoza kusamva bwino panthawi yopukuta kumbuyo kwa mphuno komanso panthawi yotenga magazi oyeza za kachirombo ka HIV ndi kuchuluka kwa tizirombo toyambitsa matendawa. Azithromycin ndi amoxicillin ndi mankhwala oti akhala akugwiritsidwa ntchito kwa nthawi yayitali m'Malawi ndipo sikweni-kweni kuyambitsa mavuto. Patali-patali azithromycin amapangitsa kumva nthumazi, ziwengo, komanso kusokonekera kwa kagwiridwe ntchito ka mtima. Patali-patali amoxicillin amapangitsa kusakhazikika mmanganizo, kumva chizungulire, komanso kutuluka ziwengo munthu akakhala padzuwa.

A London School of Hygiene ndi Tropical Medicine ali ndi thumba landalama zachipukuta misozi lokhudzana ndi kafukufukuyu. Ngati mwapweteka kapena kuvulala chifukwa chotenga nawo mbali mu kafukufukuyu, mudzakhale omasuka kupempha chipukuta misonzi.

Kodi padzakhala zopindula zina zilizonse mu kafukufukuyu?

Chopindulitsa chodziwika cha kafukufukuyu ndi chakuti mudzakhala ndi mwayi oyezedwa matenda a chifuwa chachikulu mozama kuposa m'mene zimakhalira nthawi zonse. Zimenezi zidzakuthandizirani kudziwa ngati muli ndi matenda a chifuwa chachikulu komanso kukhala ndi mwayi oyamba kulandira thandizo la mankhwala a chifuwa chachikulu. Kafukufukuyu ndi opindindulitsanso kwa opereka chisamaliro cha kuchipatala chifukwa adzayankha mafunso ofunikira okhudzana ndi kagwiritsidwe ntchito ka mankhwala opha tizirombo toyambitsa matenda panthawi ya ndondomeko yoyeza matenda a chifuwa chachikulu.

Kodi zotsatira za mukafukufukuyu zidzakhala za chinsinsi?

Chizindikiritso chanu mu kafukufukuyu chidzatengedwa kukhala cha chinsinsi. Zotsatira za kafukufukuyu, zikhoza kudzasindikizidwa ndi cholinga cha sayansi koma dzina lanu kapena chizindikiritso chilichonse chokhudzana ndi inu chidzabisidwa. Uthenga okhudza zotsatira zoyesa matenda achifuwa chachikulu kapena HIV zidzalembedwa pogwiritsa ntchito nambala yanu yakafukufuku. Komabe, zina zomwe mungatifotokozere zitha kudzagwiritsidwa ntchito ndi amene ali oyang'anira za kafukufuku wa zaumoyo (COMREC) komanso LSHTM. kapena ndi mamembala a gulu la kafukufukuyu. Zolembedwazi zidzasungidwa mumalo otsekedwa bwino ku sukulu ya ukachenjede ya Malawi College of Medicine. Uthenga ndi zoyesa zotengedwa mu kafukufukuyu zidzassungidwa kwa zaka pafupi-fupi khumi (10) pakutha pakuyesaku, malingana ndi ndondomeko ya bungwe lathu. Zoyesa zotengedwazi ndi mauthenga ena zikhoza kugwiritsidwanso ntchito pa kafukufuku wamtsogolo ngati mutatipatsa chilolezo chimenecho.

Kodi ndikhoza kusiya kafukufukuyu nthawi ina iliyonse ndipo zimenezi zingadzakhudze thandizo langa la mankhwala?

Muli ndi ufulu kusankha kutenga nawo mbali kapena kusatenga nawo mbali mu kafukufukuyu. Ngakhale tingakonde kuti mutenge nawo mbali mu kafukufukuyu mpaka ku mapeto, kutuluka nthawi iliyonse mukafukufuku ndi chisankho chanu popanda chilango chilli chonse kapena kuluza kulandira thandizo lililonse lomwe mukuyenera kulandira. Munthawi yakafukufukuyu, tidzakudziwitsani patati

patuluka mauthenga ena a sayansi ofotokoza zinthu zimene zingakupangitseni kuti mulingalirenso zachisamkho chanu chotenga nawo mbali.

Kodi pali phindu la ndalama lotani pakutenga nawo mbali mu kafukufukuyu?

Sipadzakhala kupatsidwa malipiro chifukwa chotenga nawo mbali mukafukufukuyu. Ndalama yomwe tidzakupatseni ndi yokwana MK8,000. Ndalamayi tizikupatsani pangonopango pamasiku anu akafukufuku..

Kodi kafukufukuyu ndiwovomerezeka ndi komiti yowona za ufulu wa anthu mukafukufuku?

Kafukufukuyu wavomerezedwa ndi London School of Hygiene & Tropical Medicine Research Ethics Committee, ndi College of Medicine Research Ethics Committee (COMREC).

Kodi mungafunse ndani ngati muli ndi mafunso okhudzana ndi kafukufukuyu?

Ngati muli ndi mafunso ena aliwonse okhudza kutenga nawo mbali mukafukufukuyu, chonde khalani omasuka kundifunsa. Munjira ina, mukhoza kulumikizana ndi anthu otsatirawa pa lamya kapena polemba kalata kumakeyala awa:

	Name **Dzina**	**Telephone** **Lamya**	**Postal address** **Adilesi**
Study investigators Akulu-akulu akafukufuku	Dr Titus Divala	0999478376	Helse Nord Tuberculosis Initiative University of Malawi College of Medicine
	Dr Marriott Nliwasa	0888681948	Private Bag 360, Chichiri, Blantyre 3, Malawi
COMREC	Administrative officer, COMREC Secretariat	01 877 245 01 877 291	University of Malawi College of Medicine Private Bag 360, Chichiri, Blantyre 3, Malawi

Kodi pali phindu lotani komanso zotsatira zosayembekezereka zotani pogwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ngati njira yothana ndi matenda a chifuwa chachikulu mu anthu amene ali ndi chifuwa?

Chitsimikizo cha odwala

Lembani mubokosi liri kumanjali mawu oyamba adzina lanu kapena dindani ndi chala ngati mukuvomereza

Mfundo yachitsimikizo	
Ndikutsimikiza kuti ndawerenga chikalata cha uthenga wa kafukufuku amene watchulidwa m'mwambamu. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira. KAPENA Ndafotokozeredwa uthengawu ndi akafukufuku mu chilankhulo chimene ndikuchimvetsa. Ndakhala ndi mwayi woganizira za uthengawu, kufunsa mafunso komanso ndayankhidwa mokhutira.	
Ndikumvetsa kuti kutenga nawo mbali kwanga ndikosakakamizidwa ndipo ndili ndi ufulu kusiya panthawi ina iliyonse popanda kupereka chifukwa china chilichonse, popanda kukhudza chisamaliro cha kuchipatala kapena ufulu wanga.	
Ndikumvetsa kuti magawo ofunikira a zolembedwa zanga za ku chipatala komanso mu kafukufukuyu kuwonedwa ndi anthu ovomerezeka aku LSHTM, University of Malawi College of Medicine komanso COMREC, pamene kuli kofunika kutenga nawo mbali mukafukufukuyu. Ndikupereka chilolezo kwa anthu amenewa kuti athe kuwona za zolembedwa zanga.	
Ndikumvetsa kuti zomwe atolere akafukufuku zokhudza ine zikhoza kugawilidwa kwa anthu ena opanga kakafukufuku, ndipo kuti sipadzakhala chizindikiro chilichonse chosonyeza kuti zinachokera kwa ine.	
Ndikumvetsa kuti zoyeza za mthupi mwanga zimene zidzatengedwe kwa ine zidzagwiritsidwa ntchito kuthandizira kafukufuku wina mtsogolo, ndipo zikhoza kudzagawidwa mwachinsinsi ndi akafukufuku ena, pa ntchito yawo yovomerezeka ndi malamulo aowona zakafukufuku.	
Ndikuvomereza kutenga nawo mbali mu kafukufuku amene watchulidwa pamwambayu.	

Dzina la wotenga nawo mbali **Sayini/chidindo cha chala cha wotenga mbali** **Tsiku**

Dzina la mboni yopanda mbali* **Sayini ya mboni yopanda mbali** **Tsiku**

Ndikutsimikiza kuti ndafotokoza za uthenga wa kafukufukuyu molondola kwa _____, ndipo ine zinamveka monga mwakudziwa kwanga ndi, wotenga nawo mbali komanso kuti apereka chilolezo chawo kuti atenge nawo mbali* pamaso pa mboni yopanda mbali imene yatchulidwa pamwambapa (ngati kuli koyenera).

Dzina la wotenga chilolezo **Sayini ya wotenga chilolezo** **Tsiku**

*Mboni yopanda mbali ikuyenekera kukhala yokhulupiridwa ndi munthu ofuna kutenga nawo mukafukufukuyo. Mboni ikhoza kulemba dzina la munthu ofuna kutenga nawo mukafukufukuyo koma siingasayine mmalo mwake. Munthu ofuna kutenga nawo mukafukufuku, ngati samatha kuwerenga ndi kulemba, asayine ndi chidindo cha chala chake ndipo mboni isayine dzina ndi sayini. pamalo ambone.

Mpatseni otenga nawo mbali chikalata chimodzi kuti chikhale chake

Dzina la kafukufuku: Kodi kugwiritsa ntchito mankhwala opha tizirombo toyambitsa matenda ena ngati njira yothandizira kufufuza chifuwa chachikulu kuli ndi phindu kapena kuipa kotani?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	30
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	26

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4, 8, 22
Objectives	#7	Specific objectives or hypotheses	5, 10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, 6

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care	15

		providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P30, appendix (protocol)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P30, appendix (protocol)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P30, appendix (protocol)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	30 appendix (consent)
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	30 appendix (consent)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	30 appendix (consent)
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	30, appendix (protocol)
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	30, appendix (protocol)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25, and 28 appendix (protocol)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25, and 28 appendix (protocol)

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	30 appendix (consent)
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	30 appendix (consent/protocol)

Notes:

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