PROTOCOL

CAPRISA 094

Triage Test for All Oral DR-TB Regimen
(TRiAD Study)

A Phase 4 operational study to assess the effectiveness, feasibility, acceptability, and cost effectiveness of the GeneXpert MTB/XDR (Xpert XDR; Cepheid) assay for rapid triage-and-treatment of DR-TB

A multi-centre, multi-country prospective cohort study

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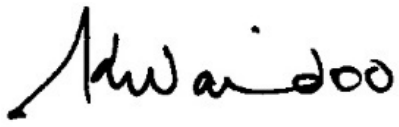
INVESTIGATOR SIGNATURE FORM
Version 5.0
04 November 2022
INVESTIGATOR APPROVAL STATEMENT

I have read the protocol and agree that it contains all necessary details for carrying out the Study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated. All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training.

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable national regulations and ICH guidelines.

Site Investigator:



_____ 28 September 2023

Principal investigator signature (CAPRISA) Date

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ABBREVIATIONS AND ACRONYMS

AE	Adverse Events
ADR	Adverse Drug Reaction
AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
AIGHD	Amsterdam Institute For Global Health And Development
ART	Antiretroviral Treatment
BDQ	Bedaquiline
BMI	Body Mass Index
BPaL	Bedaquiline-Pretomanid-Linezolid
BPaMz	Bedaquiline-Pretomanid-Moxifloxacin-Pyrazinamide
BREC	Biomedical Research Ethics
CAPRISA	Centre For The AIDS Programme Of Research In South Africa
CFZ	Clofazimine
Co – PI	Co - Principal Investigator
CRF	Case Report Form
CRS	Clinical Research Site
CT	Cycle Threshold
DAIDS	Division of Acquired Immunodeficiency Syndrome
DALY	Disability Adjusted Life Year
DLM	Delamanid
DNA	Deoxyribonucleic Acid
DR-TB	Drug-Resistant TB
DSMB	Data Safety Monitoring Board
DST	Drug Susceptibility Testing
DS-TB	Drug-Sensitive TB
E	Ethambutol
eCFU/ml	Estimated Colony Forming Units Per Millilitre
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDCTP	The European And Developing Countries Clinical Trials Partnership
EDR	Electronic Drug Resistant Software
EPHI	Ethiopian Public Health Institute
FDA	Food And Drug Administration
FIND	The Foundation For Innovative New Diagnostics
FQ	Fluoroquinolones
GCDMP	Good Clinical Data Management Processes
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
HR-TB	TB resistant to INH with no resistance to rifampicin
IATA	International Air Transport Association

ICF	Informed Consent Form
IHVN	Institute Of Human Virology Nigeria
INHhd	High-Dose Isoniazid
IRB/IEC	Institutional Review Board/Independent Ethics Committee
JSC	Joint Steering Committee
KNCV	KNCV Tuberculosis Foundation
KZN	KwaZulu – Natal
LFX	Levofloxacin
LPA	Line Probe Assay
LTBI	Latent TB Infection
LTFU	Loss To Follow-Up
LZD	Linezolid
TB-MBLA	Tuberculosis - Molecular Bacterial Load Assay
MDR-TB	Multi Drug-Resistant TB
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MMT	Medical Monitoring Team
M.tb	Mycobacterium Tuberculosis
MXF	Moxifloxacin
NGS	Next-Generation Sequencing
NHREC	National Health Research Ethics Committee
NIMR	National Institute For Medical Research
NTP	National Tuberculosis Control Programme
OCR	optical character recognition
OSR	Ospedale San Raffaele
pDST	Phenotypic Drug susceptibility testing
PTB	Pulmonary TB
PI	Principal Investigator
PID	Participant's ID
PLWHA	People Living With HIV/AIDS
PTO	Prothionamide
QA	Quality Assurance
QC	Quality Control
QTc	Quantum Tunnelling Composite
RNA	Ribonucleic Acid
rRNA	Ribosomal RNA
RR-TB	Rifampicin-Resistant TB
RT-qPCR	Reverse Transcription quantitative PCR
SA	South Africa
SA DoH	South African Department Of Health
SA GCP	South African Good Clinical Practice
SAE	Serious Adverse Events
SAPHRA	South African Health Products Regulatory Agency
SAS	Statistical Analysis Software

SERO	Scientific And Ethical Review Office
SOC	Standard Of Care
SoE	Schedule Of Events
SOP	Standard Operating Procedure
STREAM	Short Standardized Regimen For The Treatment Of Rifampicin-Resistant Tuberculosis: A Randomized Non-Inferiority Trial To Evaluate A Short Standardized Regimen For The Treatment Of Rifampicin-Resistant Tuberculosis
STR	Shorter Treatment Regimen
TB	Tuberculosis
TRD	Terizidone
TTP	Time to positivity
TRiAD	Triage Test For All Oral DR-TB Regimen
USTA	University Of St Andrews
WGS	Whole Genome Sequencing
WHO	World Health Organisation
XDR-TB	Extensively Drug-Resistant TB
Z	Pyrazinamide

1. STUDY SUMMARY

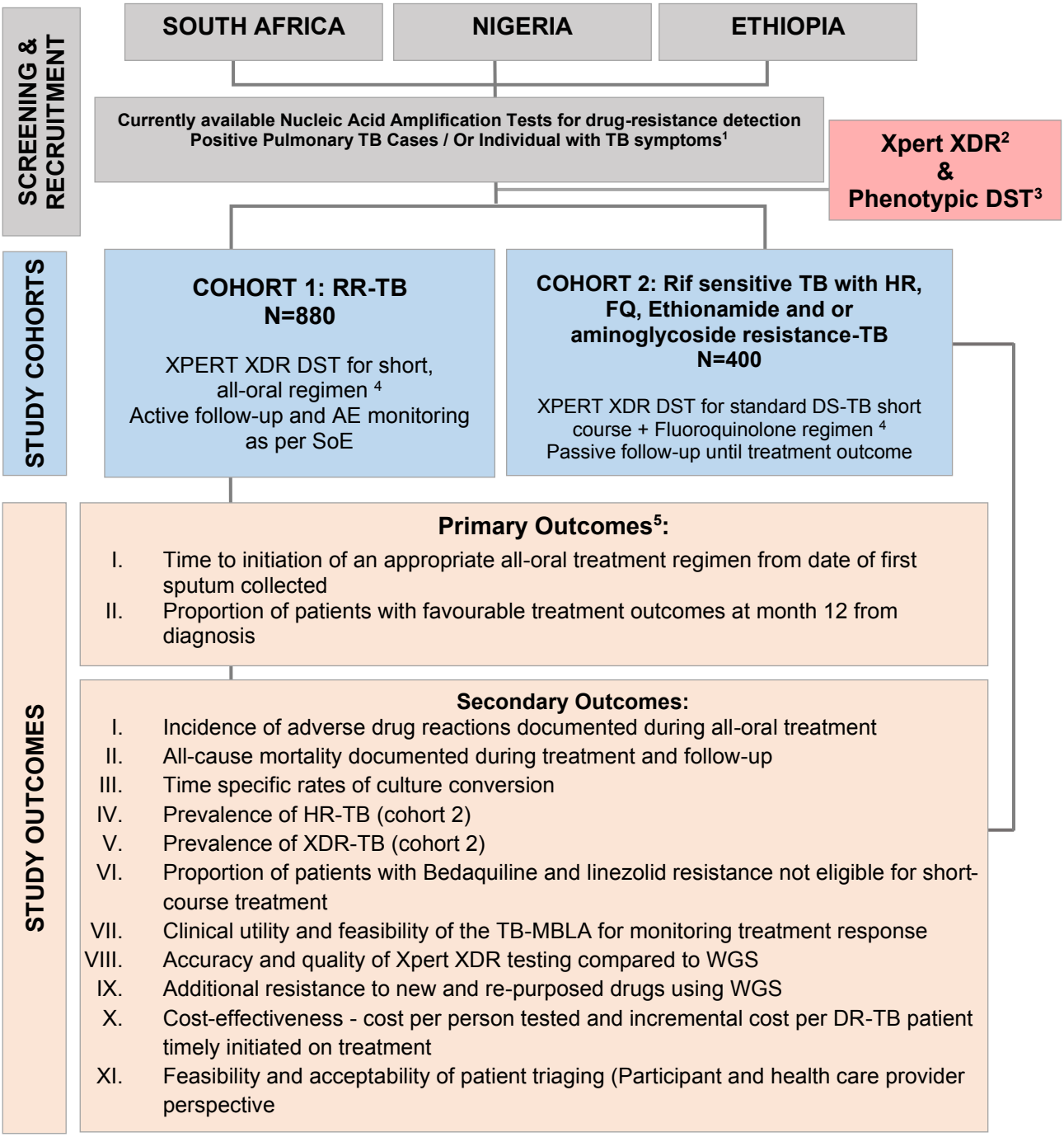
The TRiAD study is a multi-center, multi-country Prospective Pragmatic Cohort study assessing the effectiveness, feasibility, acceptability, and cost-effectiveness of implementing the Xpert MTB/XDR (Xpert XDR; Cepheid) assay for rapid triage-and-treatment with short, all-oral drug resistant tuberculosis (DR-TB) treatment. The proposed study aims to screen approximately 4800 GeneXpert MTB/RIF or Ultra MTB-positive participants or any currently available Nucleic Acid Amplification Tests for drug-resistance detection changes (irrespective of rifampicin resistance status) from clinical research sites in South Africa, Nigeria and Ethiopia to enrol 880 rifampicin resistant (RR) and 400 rifampicin sensitive and isoniazid, fluroquinolone and or second line injectable drug (SLID) resistant participants over a period of 12-18 months. The Xpert XDR assay, a rapid genotypic test, will be implemented as a reflex test to detect resistance to isoniazid, fluoroquinolones and second-line injectable agents to provide rapid genotypic susceptibility testing for DR-TB detection. Participants that test positive for *Mycobacterium tuberculosis (M.tb)* with rifampicin resistance will be enrolled in *Cohort 1* (n=880). Participants that test positive for *M.tb* that are rifampicin susceptible with isoniazid, fluroquinolone and or second line injectable drug (SLID) resistant will be enrolled in *Cohort 2* (n=400). Results from the Xpert XDR assay will be used to guide selection of appropriate, evidence-based, all-oral DR-TB treatment regimens of shortest possible duration. The tuberculosis molecular bacterial load assay (TB-MBLA) will be used as an adjunct to provide bacillary load monitoring over the course of treatment to assess real-time treatment response. Operational research will provide information about the feasibility, acceptability and cost-effectiveness to inform policies and guidelines for programmatic implementation of the triage-and-treat model.

Table 1 Overview of TRiAD Study

Study Aim	To evaluate the effectiveness, operational feasibility, acceptability, and cost-effectiveness of implementing the Xpert MTB/XDR assay for rapid triage and selection of all-oral regimens for Drug-Resistant Tuberculosis (DR-TB)
Study Design	Prospective Pragmatic Cohort Study: non-randomized interventional phase 4 (clinical access protocol) implementation science study utilizing interventions of proven clinical efficacy
Study Duration	48 months: study enrolment will occur over 12 -18 months
Sample Size	A total of 1280 participants will be enrolled between 2 prospective study cohorts: Cohort 1 (newly diagnosed DR; rifampicin resistance [RR-TB] participants; n=880) and Cohort 2 (rifampicin sensitive and isoniazid, fluroquinolone and or second line injectable drug (SLID) resistant participants; HR-TB; n=400). Data from a historical cohort (Cohort 3; n=220) of RR-TB participants that accessed DR-TB care at each implementing site *over the last 2 years (approximately 24 months)* prior to study start.

Study sites	South Africa (n=2), Nigeria (n=6) and Ethiopia (n=5)
Study population	Adult participants (18 years and over) who test positive for pulmonary *M.tb* with HR-TB or RR-TB will be approached for study participation
Study intervention	Xpert MTB/XDR assay as a triage test to guide early initiation of an appropriate all-oral DR-TB treatment regimen
Study Objectives	**Primary Objectives:** • To compare the time to initiation of resistance-pattern appropriate TB treatment from the date of first sputum collection with the standard of care compared to a historical cohort, stratified by geographical location • To assess the proportion of DR-TB participants with cure and/or DR-TB treatment completion at month 12 compared to a historical control group **Secondary Objectives:** **Clinical:** • To assess the safety and effectiveness of all-oral regimens under operational conditions • To assess all-cause mortality at month 12 and 18, rates of drug-related discontinuation for safety concerns and rates of drug-related adverse events **Microbiological:** • To assess time to culture conversion, cure, and rates of clinical TB relapse • To determine the prevalence of HR-TB stratified by geographic location • To determine the prevalence of pre-XDR and XDR-TB using phenotypic DST to bedaquiline, pretomanid and linezolid • To determine the proportion of participants with bedaquiline and linezolid resistance warranting a switch from short-course treatment • To assess the clinical utility of the TB Molecular Bacterial Load Assay (TB-MBLA) as a predictor of treatment outcome • To assess the diagnostic and clinical performance of the test and triage approach by geographic location using whole genome sequencing (WGS) and Minimum Inhibitory Concentration (MIC) analysis • To determine the phylogenetic structure and full drug resistance patterns of study samples, including bedaquiline, linezolid, levofloxacin and pretomanid

	Cost-effectiveness, feasibility and acceptability compared to the standard of care: • To determine cost per person tested and incremental cost per DR-TB participant timely initiated on the resistance-pattern appropriate regimen • To determine the incremental cost per Disability Adjusted Life Year (DALY) averted and per day delay averted in treatment with the resistance- pattern appropriate regimen • To assess programmatic cost-effectiveness, feasibility, and acceptability of implementing any currently available Nucleic Acid Amplification Tests for drug-resistance detection changes with Xpert MTB/XDR testing for HR and second-line DR-TB drugs • To investigate participant's, health care provider's and policy-maker's acceptability of the triage and treat approach • To assess the feasibility of the implementation of the triage and treat approach in routine care



[1] All currently available Nucleic Acid Amplification Tests for drug-resistance detection Positive sputum samples will be screened using Xpert XDR assay until we meet the recruitment target for cohort 2. Thereafter, only RR-TB patients will be screened for cohort 1. Xpert XDR detects resistance to INH, Fluoroquinolones and 2nd Line Injectables

[2] All eligible patients will provide an additional sputum sample for Xpert XDR testing at screening, if reflex testing on provided sputum sample is not feasible

[3] Phenotypic DST to BDQ, Linezolid and Clofazimine will be offered for pre-XDR TB cases as per in-country guidelines

[4]Choice of regimen will be guided by best available evidence from clinical trials using novel regimen, current WHO and in-country guidelines as described in Table 2

[5] Primary outcome measures for cohort 1 will be compared to a historical dataset of DR-TB patients diagnosed and treated at the each of the facilities over the last 2 years (approximately 24 months)

2. INTRODUCTION

2.1. Background and Rationale

Tuberculosis (TB) caused by the bacterium *Mycobacterium tuberculosis* (*M.tb*), remains the deadliest infectious disease globally. According to the World Health Organization (WHO) global TB report, the burden of multidrug-resistant TB (MDR-TB); i.e., resistance to at least rifampicin and isoniazid, has increased by an annual rate of over 20% during the period 2009-2017(1). In 2019, the global burden of Rifampicin-Resistant TB (RR-TB) was estimated at 465,000 cases, 78% of which was MDR-TB. Sub-Saharan Africa carries 25% of the global burden of drug-resistant TB (DR-TB) (2). Successful management of DR-TB is hampered by difficulties in both diagnosis and treatment, fuelling the ongoing transmission of DR-TB (3). In order to achieve the targets of the WHO End TB strategy by 2035, a 90% decrease in TB incidence and a 90% reduction in TB mortality is required between 2015-2035. In line with this ambitious target, there is an urgent need for new diagnostic and therapeutic approaches in order to improve the diagnostic accuracy and timely initiation of treatment for DR-TB (4).

Globally, health systems have failed to effectively implement DR-TB testing and treatment regimens, evidenced by dismal treatment success rates. In 2019, WHO reported treatment success rates of approximately 57% for DR-TB (2). Historically, the treatment of DR-TB has been challenging due to prolonged duration of treatment (20-24 months), severe toxicities and sub-optimal treatment success. Given the complex nature and duration of DR-TB treatment, significant medication adherence issues arise thereby contributing to poor treatment completion rates. Until recently, the WHO guidelines for MDR-TB (including RR-TB) and extensively drug-resistant TB (XDR-TB) incorporated the use of injectable aminoglycosides and a fluoroquinolone as the backbone of treatment (5). These agents were considered significant contributors in obtaining a successful treatment outcome. However, the use of these drugs has been associated with severe discomfort and side-effects including hearing loss and renal impairment, which, in addition to personal suffering, affect treatment adherence and completion (6). Given the toxicity associated with the second-line injectable drugs, WHO recently modified DR-TB treatment guidelines no longer recommend the use of second-line injectables as part of the MDR-TB regimen. In the latest guidelines, WHO re-classified anti-TB drugs into three main groups according to the available evidence on DR-TB drug effectiveness and safety. These include; Group A (bedaquiline, linezolid, moxifloxacin or levofloxacin), Group B (clofazimine, and cycloserine or terizidone) and Group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin/streptomycin, ethionamide/prothionamide, p-aminosalicylic acid). In line with this recommendation the definition of XDR-TB on the basis of resistance to second-line injectables became less clinically relevant. Thus, leading to 2021 revised definitions for DR-TB. According to the update, pre-XDR is defined as RR-TB or MDR-TB with additional resistance to a fluoroquinolone. XDR-TB is now defined as RR-TB or MDR-TB with resistance to a fluoroquinolone and at least one other group A drug. The definition for MDR-TB remains the same.

The diagnosis of DR-TB poses a further obstacle to attaining successful treatment. In high-burden DR-TB countries, the diagnosis of MDR-TB in most settings is a proxy diagnosis made

through a multi-step testing cascade. Currently, the front-line molecular diagnostic assay for drug resistance is Cepheid Xpert MTB/RIF or Xpert MTB/Ultra, which detects the presence of *M.tb* bacilli and simultaneously detects RR-TB. Whilst rapidly identifying patients eligible for MDR-TB treatment, the test is limited to the detection of RR only (7, 8). Patients who display RIF resistance receive reflex testing which includes resistance to fluoroquinolones and second-line injectables using standard phenotypic drug susceptibility testing (pDST) and the Hain Line Probe Assays (LPA 1 and 2), which detect resistance to isoniazid, rifampicin, fluoroquinolones and second-line injectable agents (9). Drug susceptibility testing (DST) for all other drugs is conducted using phenotypic testing methods. However, following a rapid diagnosis by Xpert MTB/RIF or Xpert MTB/Ultra, all follow-on testing is conducted at a regional laboratory thereby increasing the turn-around times for providing a comprehensive resistance profile. Furthermore, these DST methods have several limitations. Although LPA testing can be rapidly performed on sputum samples, LPAs require specialised laboratory facilities, longer turnaround time and are associated with a high indeterminate rate (~30%) in smear-negative patients (10). Phenotypic DST (pDST) techniques require approximately 4-6 weeks and result interpretation are compounded by issues with the established critical drug concentrations used to predict resistance and poor performance for certain drugs such as ethionamide and pyrazinamide. Currently, DR-TB patients are initiated on empiric treatment, which is modified as DST results become available, resulting in a 4-6-week delay in initiation of appropriate treatment. As a result of this sub-optimal testing cascade, many patients may receive a limited number of effective drugs in the regimen, increasing the risk of amplifying drug resistance and ongoing transmission of DR-TB (3). A further challenge which hinders the diagnosis and treatment of DR-TB is the lack of susceptibility testing for isoniazid resistance by assays available at the point where the patient enters the care cascade, i.e. Xpert MTB/RIF, Xpert MTB/RIF Ultra, or the Truenat assays. As a consequence, isoniazid mono-resistant TB patients (HR-TB; i.e. patients who display INH resistance in the absence of RIF resistance) are not appropriately diagnosed. This sub-set of patients receive standard DS-TB treatment, thereby increasing the risk of amplifying drug resistance (11).

In the last few years, the DR-TB treatment landscape has been transformed drastically by several landmark changes to DR-TB guidelines. These include: reports confirming safety and the survival benefit of Bedaquiline (BDQ) for MDR-TB (12); WHO endorsement of the standard 9 month short-course regimen for MDR-TB and the Short Standardized Regimen For The Treatment Of Rifampicin-Resistant Tuberculosis (STREAM ; NCT02409290) study results demonstrating non-inferiority of shorter DR-TB regimens to longer regimens (13, 14); the replacement of second-line injectables with BDQ in the standard short-course DR-TB regimen, resulting in the first all-oral regimen for DR-TB (15); and the results of the novel 6 month BPaL (BDQ, pretomanid, and linezolid) regimen for XDR-TB. These changes have resulted in a rapid transition to all-oral treatment options for DR-TB. Thus, the current study aims to implement diagnostics with proven clinical efficacy to guide treatment with novel, all-oral regimens as efficacy data from clinical studies emerge. Furthermore, the lack of specific outcome data for the novel diagnostic assays represents a significant implementation research gap which the study will address. Given the state of access to DR-TB diagnosis and treatment globally, the implementation of shorter, efficacious, and more importantly, less toxic regimens than the conventional long regimen holds significant promise in improving dire treatment success rates. Notably, this approach could potentially preserve the potency of the new drugs included in the shorter regimens by preventing the rapid amplification of resistance.

2.2. Epidemiology of DR-TB

South Africa, Ethiopia and Nigeria feature prominently among the 30 high-burden TB countries with significantly overlapping epidemics of TB, Human Immunodeficiency Virus (HIV) and MDR-TB. The 30 high-burden countries collectively contribute to approximately 90% of the global disease burden. South Africa, in particular, remains among the few countries with a TB incidence exceeding 500 cases per 100,000 population with approximately 360,000 cases of TB reported during 2019. In 2019, 13,005 and 406 cases of laboratory confirmed RR/MDR-TB and XDR-TB were reported in South Africa, respectively. The overall treatment success rate was 71% for drug-susceptible TB (DS-TB), 60 % for RR-TB/ MDR-TB and XDR-TB. Ethiopia has a TB incidence rate of 140 cases per 100,000 population with approximately 157,000 cases of TB reported during 2019. In 2019, 658 and 4 cases of laboratory confirmed RR/MDR-TB and XDR-TB were reported in Ethiopia, respectively. The overall treatment success rate was 88% for DS-TB, and 75% for RR-TB/ MDR-TB and XDR-TB. Nigeria records a TB incidence rate of 219 cases per 100,000 population with approximately 440,000 cases of TB reported during 2019. In 2019, 2,384 and 16 cases of laboratory confirmed RR/MDR-TB and XDR-TB were reported in Nigeria, respectively. The overall treatment success rate was 87% for DS-TB, 77% for RR-TB/ MDR-TB, and no data were available for the XDR-TB patients (2).

2.3. Evidence for novel regimens and diagnostics proposed in this study

2.3.1. Novel, all-oral treatment regimens for DR-TB

Historically, MDR-TB and XDR-TB patients have been treated with a multi-drug treatment regimen which comprises of an intensive phase of treatment of 8 months and a total duration of treatment of 20-24 months. For patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and for whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter treatment regimen (STR) still including an injectable, was recommended. This STR was evaluated in Stage 1 of the STREAM trial and is composed of high-dose later generation fluoroquinolone, clofazimine, pyrazinamide and ethambutol throughout, supplemented by amikacin, prothionamide, and high-dose isoniazid in the intensive phase. The treatment duration of the intensive phase is four months (extended to a maximum of six months until sputum smear conversion), and the duration of the continuation phase is five months. In December 2019, WHO issued a rapid communication encouraging countries to replace the injectable in this regimen with BDQ and use the all oral bedaquiline based STR as the preferred option.

In addition to this newly recommended shorter all-oral MDR-TB regimen, there are other shorter regimens currently being evaluated in clinical trials for the same and different patient groups. Many of these regimens employ new or repurposed medicines, which have been shown to be effective in clinical trials. These regimens have common desirable features: good tolerability, all-oral and with shorter treatment duration.

One such regimen is the BPaL regimen which consists of BDQ, pretomanid and linezolid given for 6 months. Currently, the BPaL regimen is the most appropriate alternative for the treatment of pre-XDR TB (MDR with additional fluoroquinolone resistance) and XDR-TB (pre-XDR with resistance to at least one additional Group A drug). The efficacy of the regimen was evaluated

in a single-arm randomized controlled trial which demonstrated that 90% of patients recorded a favourable treatment outcome. Treatment associated toxicity linked to the use of linezolid within the regimen was reported as manageable with dose reduction and interruption of linezolid use (16). The BPaL regimen recently received Food And Drug Administration (FDA) approval for use in people with DR-TB or treatment-intolerant/non-responsive MDR-TB or patients for whom there is no other viable as per WHO recommendations (17).

Another novel, short-course regimen under evaluation is the BPaMZ regimen indicated for use in HR-TB, RR-TB and MDR-TB is currently in late-stage clinical development. The regimen incorporates the use of two novel drugs, BDQ and pretomanid, in combination with pyrazinamide and moxifloxacin (SimpliciTB study). Pre-clinical data in a murine model demonstrated potent sterilising activity (18). Phase 2B human study data indicates superior efficacy of the novel combination in patients with DS-TB and MDR-TB (19). A phase 3 trial of the BPaMZ regimen (SimpliciTB; NCT03338621) is currently evaluating the potential to both shorten treatment to 4 months for patients with DS-TB and also effectively treat patients with RR- or MDR-TB (as a 6-month regimen, because of the higher risk of associated resistance to pyrazinamide) (20). Modelling analysis on the projected patient outcomes using the BPaMZ regimens indicates that universal implementation of the regimen has the potential to increase the percentage of patients with RR-TB who are cured from 60% to nearly 90% and maintain nearly 90% cure among patients with DS-TB. Further, the regimen could reduce treatment duration by two months and reduce infectious person-time by 50% (RR-TB) (21).

The current programmatic DR-TB treatment regimens for each country and the proposed novel interventions are described in Table 2. Novel DR-TB regimens under evaluation will be considered for inclusion by the TRiAD Joint Steering Committee (JSC) once sufficient safety and efficacy data becomes available.

2.3.2. The Xpert MTB/XDR Assay

The GeneXpert instrument platform is an automated cartridge-based system for TB diagnosis. The WHO endorsed the use of the Xpert MTB/RIF assay for the GeneXpert platform in 2010 and the assay has since been widely used in TB programs. The Xpert MTB/RIF assay was subsequently replaced by the Xpert Ultra assay which demonstrated improved sensitivity in paucibacillary disease. However, for RR-TB patients, the Xpert MTB/RIF and Ultra assays provide no further information on the resistance profile of the infecting strain type.

The Xpert MTB/XDR cartridge, a new diagnostic that is being evaluated in this study, intended for use as a reflex test. The assay includes eight genes and promoter regions in *M. tb* allowing for the detection of resistance to isoniazid, aminoglycosides and fluoroquinolones, ethionamide and the second-line injectables, enabling the diagnosis of pre-XDR TB in combination with Xpert MTB/RIF or Ultra. This assay showed excellent analytical performance in a clinical study performed at two sites with 100 sputum and 214 clinical isolates. The assay demonstrated a sensitivity of 94-100% and a specificity of 100% for all drugs except for ethionamide in comparison to sequencing. The sensitivity and specificity when compared to phenotypic drug-susceptibility testing (DST) were in the same range (22, 23).

The Xpert MTB/XDR assay is undergoing external assessment in the Xpert MTB/XDR clinical evaluation trial (NCT03728275), wherein the diagnostic accuracy of the assay and its use in diverse clinical settings is being evaluated amongst 600 patients in multicentre clinical evaluation (20). The MTB/XDR assay incorporates the same single-step specimen processing as the Xpert MTB/RIF and Ultra and can be implemented with minimal staff training and biosafety requirements. Existing GeneXpert instruments have the potential to be upgraded contemporaneously by upgrading software and performing a 10-colour calibration. These are significant features that would permit Xpert MTB/XDR to be used in peripheral sectors of the global health care system, where more rapid identification of expanded drug resistance may improve therapeutic decision-making. WHO has endorsed the use of Xpert XDR for diagnosis of TB drug resistance as of June 2021 (**https://www.who.int/publications/i/item/9789240029415**).

The focus of this protocol is to utilise the Xpert MTB/XDR assay to triage participants by promptly identify varying resistance profiles in order to guide the selection of appropriate treatment regimens. With optimal implementation, this new test should improve the selection of appropriate regimens, reducing time to appropriate treatment and improving patient outcomes (22, 24). Given the recent updated definition, the Xpert XDR assay will diagnose pre-XDR-TB. Additional DST to BDQ and linezolid (LZD) is required to define XDR-TB.

2.3.3. Tuberculosis-Molecular Bacterial Load Assay (TB-MBLA)

The TB-MBLA is a novel, quantitative Reverse Transcription PCR (RT-qPCR) that uses 16S-ribosomal RNA (rRNA) targets to quantify the *M.tb* bacillary load over the course of treatment in real-time (25). A major limitation of the current TB diagnostic and management algorithm is the lack of a sensitive and rapid assay for evaluation of treatment efficacy and predicting treatment response. Current therapeutic monitoring is dependent on *M.tb* bacterial load monitoring from clinical samples inferred from Mycobacteria Growth Indicator Tube (MGIT) time to a positive result (TTP) and smear microscopy. This poses a challenge as most settings where patients first enter the care cascade have limited availability of culture resources due to the cost of specialised laboratory infrastructure and training requirements. When resources are available, culture-based results are not always made available in a clinically relevant timeline to inform timely clinical decision making. This is compounded by factors such as specimen transport, type of media, and decontamination to eliminate non-mycobacterial flora which compromise the consistency of culture.

In addition, culture time-to-result is long and depends on the patient TB bacillary burden. This means that patients with a lower bacillary burden wait longer for results than patients presenting with a higher bacillary burden. Further, sputum culture conversion is only weakly predictive of long-term patient outcome for regimens but not individuals, limiting its utility to individual and clinical trial management. Smear microscopy, an approved routine treatment monitoring method, is less sensitive and cannot distinguish viable and dead bacilli. The TB-MBLA uses abundant 16S-rRNA as a target and can accurately quantify *M.tb* viable bacillary load directly from patients' sputum over many weeks of treatment and has the potential to replace culture, offering a promising solution and improved precision in clinical care. The assay rapidly measures patient tuberculosis bacillary burden and its change in response to anti-TB therapy, enabling the clinician to make an informed decision on patient progress. This

ability avoids challenges related to culture (e.g. time to results and contamination) and gives TB-MBLA the potential to eventually replace microscopy and culture for treatment response monitoring (26-28).

To date, the assay has been evaluated in three high TB burden, low-resource settings in Africa through the European and Developing Countries Clinical Trials Partnership (EDCTP) funding. The data showed that TB-MBLA reduces time to detection of *M. tb* bacillary loads from weeks to hours, reproducible in different laboratory settings and has the potential to inform real time clinical decision of patient treatment and expedite TB drug trials (29). Furthermore, bacillary load measured by TB-MBLA concurs with bacillary load measured by standard MGIT culture (30) and can accurately distinguish the bactericidal effect of different anti-TB regimens (31). The current study provides a unique opportunity to evaluate the role of TB-MBLA in monitoring treatment response in participants receiving varying DR-TB regimen.

2.4. Potential Benefits

There will be a direct benefit to patients who participate in this study. Participants will have access to novel drugs, diagnostics and improved treatment monitoring, not otherwise available through standard of care practice. We believe that the diagnostic methods and drugs used in this study could significantly improve TB treatment outcomes. Additionally, a rapid diagnosis coupled with initiation of appropriate treatment could potentially reduce the number of participants that are lost in the care cascade during this period. Generating evidence through implementation research on the feasibility, acceptability and cost effectiveness of novel diagnostics in improving DR-TB outcomes will fast-track translation of these study findings into policy and practice for maximum public health benefit. Given the development of the novel tests and the importance of the public health approach in triaging DR-TB participants to suitable all-oral regimens, a study evaluating the strategy is warranted. Finally, given the delays in DR-TB diagnosis, and appropriate treatment initiation, high toxicity of drugs in use, identifying strategies to improve DR-TB outcomes are important to the success of TB programmes globally.

2.5. Potential Harm

Diagnostics

The risk benefit ratio will vary by each type of resistance pattern detected. Detection of resistance conferring mutations to multiple drug classes would be beneficial to those infected with these strain types compared to those without any detectable resistance. Use of the Xpert MTB/XDR diagnostic and translation of test results for treatment modification does not preclude access to all other available diagnostic tests for DR-TB in the study settings. Until this study is completed, there is no way of knowing for sure whether a novel diagnostic that guides use of short-course DR-TB treatment will improve treatment outcomes in DR-TB participants. For this reason, there is a risk that one could be receiving DR-TB drugs that may not be beneficial.

Therapeutics

Risk of treatment related toxicity with DR-TB medication is the same for all participants exposed to given DR-TB regimen. These risks include drug toxicities from DR-TB medication

and drug interactions (e.g., between DR-TB treatment and Antiretroviral Treatment). While this study will be using several new drugs in novel regimens, stringent safety assessments from human trials conducted using these regimens have been documented and will be closely monitored. Several strategies have been implemented within this study to ensure safety of all participants should we identify any safety concerns. These include; clinical observation and referral for clinical care should participants experience untoward adverse events, safety monitoring and reporting in real time to the study safety monitoring committee and external review of all safety reports by local ethics committees and independent Data Safety Monitoring Board (DSMB).

3. DEFINITIONS OF DR-TB

- HR-TB is defined as resistance to at least isoniazid without rifampicin resistance
- RR-TB is defined as resistance to at least rifampicin without isoniazid resistance

Definitions of MDR-TB, pre-XDR and XDR-TB in background sections of this protocol refer to old WHO definitions:

- MDR-TB; resistance to at least rifampicin and isoniazid
- Pre XDR-TB; strains that fulfil the definition of MDR-TB with additional resistance to the aminoglycosides or fluoroquinolones
- XDR-TB; strains that fulfil the definition of MDR-TB with additional resistance to the aminoglycosides and fluoroquinolones.

For the purpose of defining DR-TB categories in the current study we will utilise updated 2021 WHO definitions to categorise pre-XDR-TB and XDR-TB (32)

- Pre-XDR TB; strains that fulfil the definition of RR-TB/MDR-TB with additional resistance to any fluoroquinolone
- XDR-TB; strains that fulfil the definition of RR-TB/MDR-TB with additional resistance to any fluoroquinolone and at least one additional group A drug (BDQ or LZD).

4. STUDY DESIGN, AIMS AND OBJECTIVES

4.1. Study Design

The study is a Prospective Pragmatic Cohort Study with a before-and-after study design

4.2. Study Aim

The overarching aim of the TRiAD study is to evaluate the effectiveness, operational feasibility, acceptability, and cost-effectiveness of implementing the Xpert MTB/XDR for rapid triage and selection of all-oral regimens for DR-TB.

4.3. Primary Objectives:

- To compare the time to initiation of resistance-pattern appropriate TB treatment from the date of first sputum collection with the standard of care compared to a historical cohort, stratified by geographical location
- To assess the proportion of DR-TB participants with cure and/or DR-TB treatment completion at month 12 compared to a historical control group

4.4. Secondary Objectives:

4.4.1. Clinical

- To assess the safety and effectiveness of all-oral regimens under operational conditions.
- To assess all-cause mortality at month 12 and 18, rates of drug/regimen discontinuation for safety concerns, rates of drug-related adverse events

4.4.2. Microbiological

- To assess time to culture conversion, cure, and rates of clinical TB relapse
- To determine the prevalence of HR-TB stratified by geographic location
- To determine the prevalence of pre-XDR and XDR-TB using phenotypic DST to bedaquiline, pretomanid and linezolid
- To determine the proportion of participants with bedaquiline and linezolid resistance warranting a switch from short-course treatment
- To assess the clinical utility of the TB Molecular Bacterial Load Assay (TB-MBLA) as a predictor of treatment outcome
- To assess the diagnostic and clinical performance of the test and triage approach by geographic location using whole genome sequencing (WGS) and Minimum Inhibitory Concentration (MIC) analysis
- To determine the phylogenetic structure and full drug resistance patterns of study samples, including bedaquiline, linezolid, levofloxacin and pretomanid

4.4.3. Cost-effectiveness, feasibility and acceptability compared to the standard of care

- To determine cost per person tested and incremental cost per DR-TB participant timely initiated on the resistance- pattern appropriate regimen
- To determine the incremental cost per DALY averted and per day delay averted in treatment with the resistance- pattern appropriate regimen
- To assess programmatic cost-effectiveness, feasibility, and acceptability of implementing any currently available Nucleic Acid Amplification Tests for drug-resistance detection changeswith Xpert MTB/XDR testing for HR and second-line DR-TB drugs
- To investigate participant's, health care provider's and policy-maker's acceptability of the triage and treat approach
- To assess the feasibility of the implementation of the triage and treat approach in routine care

4.5. Study Outcome Measures

Primary Outcomes:

- Time to initiation of resistance-pattern appropriate TB treatment from the date of first sputum collection
- Proportion of participants with favourable treatment outcome as defined in section 9.3

Secondary Outcomes:

- Incidence of adverse drug reactions documented during all-oral treatment under operational conditions (cohort 1 and 2)
- All-cause mortality for the duration of treatment and follow-up (cohort 1 and 2)
- Time to sputum (culture) conversion (cohort 1 and 2)
- Prevalence of HR-TB (cohort 1)
- Prevalence of XDR-TB (cohort 2)
- Proportion of participants with BDQ and LZD resistance not eligible for short-course treatment
- Clinical utility and feasibility of TB-MBLA for bacteriological follow-up in DR-TB treatment (assessment of viable bacterial load trajectories in response to treatment) (cohort 1)
- Accuracy and quality of Xpert XDR testing (cohort 1 and 2)
- Additional resistance to new and repurposed drugs (cohort 1 and cohort 2)
- Cost effectiveness (cost per person tested and incremental cost per DR-TB participant timely initiated on appropriate treatment) (cohort 1 and 2)
- Feasibility and acceptability of participant triaging (participant, health care provider and policy makers' perspective) with enablers and barriers for implementing the algorithm (cohort 1 and 2)
- Operational feasibility of Xpert XDR testing (infrastructure and human resource requirements) (cohort 1 and 2)

5. STUDY INTERVENTION

There are 3 study interventions:

1. The Xpert MTB/XDR assay will be used as a diagnostic adjunct to any currently available Nucleic Acid Amplification Tests for drug-resistance detection changesto screen participants. The Xpert MTB/XDR assay will enable prompt identification of the following DR-TB participant categories:

    a. HR-TB
    b. Rif mono-resistant TB
    c. MDR-TB
    d. Additional fluoroquinolone (FQ) resistance, i.e., pre- XDR TB

2. Early initiation of the most appropriate, evidence-based DR-TB regimen. This will be guided by the TB resistance pattern categorization from the Xpert MTB/XDR diagnostic.

Choice of DR- TB regimen will be determined by:

a. Best available evidence generated from use of novel regimens as they become available, or
b. Current WHO and in-country guidelines (Table 2).

3. In parallel, the TB-MBLA will be used to provide real-time bacillary load monitoring over the course of treatment to assess response to treatment.

Table 2: Current Drug-Resistant TB Treatment Regimen by TB resistance profile and proposed study approach

	Regimen class	Current Recommended Regimen with Duration (months) by Drug resistance profile per participating country	Proposed All-oral regimen[#]
Current Guidelines on DR- TB treatment	HR-TB	RHZE + Lfx (6)	RHZE + Lfx (6) [#]
	RR-TB and MDR-TB Short- Course Regimen	*All oral regimen:* SA: (4-6)BDQ-Lfx (or MXF)- LZD, INHhd-CFZ-E-Z/ (5) LFX-CFZ-E-Z Nigeria: (4-6)BDQ-MFX-HH-PTO-CFZ-E-Z/ (5)BDQ (2) MFX-CFZ-E-Z Ethiopia:(4-6)AM-MFX-CFZ-HH-PTO-E-Z/ (5)MFX-CFZ-E-Z ***or*** *Injection-based regimen:* (4)AMK-MFX-CFZ- INHhd -PTO-E-Z/(5) MFX-CFZ-E-Z	BDQ based all-oral regimen[#]
	RR-TB; MDR-TB; and PreXDR-TB *(Second-line resistance)* Long all-oral Regimen* :	SA: (6)BDQ-LFX-CFZ-LZD/(12)LFX-CFZ- LZD Nigeria: (6)BDQ-MFX-CFZ-LZD/ (12) MFX- CFZ-LZD Ethiopia: (6) BDQ-LFX-LZD-CFZ-CS/(14) LFX- LZD-CFZ-CS	BPaL[#]
	PreXDR-TB *(FQ resistance)* and XDR-TB# Long Individualised Regimen*:	SA: (6-8)BDQ-CFZ-LZD-DLM-TRD/(12)CFZ-LZD-TRD-Z- INHhd Nigeria: (6)BDQ-CFZ-LZD-CS/ (12)CFZ-LZD- CS Ethiopia: (BDQ)-(LFX)- (MFX)-(LZD)-(CFZ)-(CS)- (DLM)-(PTO)-(Z)-(AM)-(S)-(PAS)	BPaL[#]

Abbreviations: HR-TB, Isoniazid Mono-Resistant TB; RR-TB, Rifampicin-Resistant TB; MDR-TB, Multi Drug-Resistant TB; XDR, Extensively Drug-resistant TB, SA, South Africa, LFX, levofloxacin; BDQ, Bedaquiline; MXF, moxifloxacin; LZD, linezolid, INHhd, high-dose isoniazid; CFZ, clofazimine; E, ethambutol; Z, pyrazinamide; PTO, protionamide; DLM, Delamanid; TRD, Terizidone, BPaMz, Bedaquiline -Pretomanid-Moxifloxacin-Pyrazinamide ; BPaL, Bedaquiline -Pretomanid-Linezolid

* Longer regimens recommended when the construction of MDR/RR-TB regimen with 3 group A and 2 group B drugs is not possible due to intolerance to the medicines, acquired additional resistance etc.

[#] Regimen selection based on WHO approved all-oral regimen or the best available evidence-based regimen; once results for proposed BPaMz and ZeNIX Formal amendments will be submitted for review upon consideration of additional regimens for the use in the study

6. INVESTIGATIONAL PLAN

6.1. Selection of study clinical research sites

Countries were selected based on background disease burden of DR-TB and represent a diverse participant population, DR-TB patterns, and laboratory capacities. Clinical research sites (CRS) within countries were selected to ensure sufficient numbers of DR-TB cases to meet recruitment targets. Participants will be enrolled in nine clinical research sites. These are located in South Africa (n=2), Nigeria (n=6) and Ethiopia (n=5) (Figure 2). *Addition of clinical research sites in the study will be based on the ability to meet the enrolment targets for each country. All new clinical research sites will be approved by the in-country local IRB.*

Figure 2: Map of TRiAD Clinical Research Sites in South Africa, Nigeria and Ethiopia

6.2. Selection of Participants

Approximately 4800 participants will be screened across the 13 sites (in South Africa, Nigeria and Ethiopia) to enrol 1280 eligible participants. All presumptive TB patients presenting for diagnosis at the study sites will be approached for screening. Each of the sites will also contribute to the historical cohort as described below.

6.2.1. Selection of cohort 1

880 RR-TB (n=440 in SA, n=220 in Nigeria and n=220 in Ethiopia) participants will be enrolled into Cohort 1. Each participant in cohort 1 will be followed up for the duration of TB treatment and passively thereafter to a maximum of 18 months from TB treatment initiation.

6.2.2. Selection of cohort 2

400 HR participants into Cohort 2 (n=200 in SA, n=100 in Nigeria and Ethiopia). Each participant in cohort 2 will be followed up passively for the duration of TB treatment and passively thereafter to a maximum of six months.

6.2.3. Selection of Historical Cohorts

Each CRS will build a dataset of historical RR-TB participants that were diagnosed and started on treatment within 12 - 18 months prior to starting enrolment of the study at each of the clinical research sites. Clinical and laboratory data from this retrospective cohort will be obtained from treatment registers, participant charts and laboratory databases at each of the clinical research sites. The following data variables will be extracted: date of birth, or age, sex, HIV and ART status, facility or clinic, year and month of treatment, type of DR-TB, certainty of diagnosis (confirmed by DST or presumed, i.e., contact of DR-TB source case or failing adherent first-line TB treatment), disease classification, treatment start date and any bacteriological results on treatment (date, mycobacterial culture, DST and genotypic results), where relevant. Data on all drugs from previous DR-TB treatment regimen, DR-TB Outcomes: cure, completion, default, death, loss to follow up (LTFU) will be abstracted. Historical data will be collected on specially designed case report forms (CRF) and will be subject to routine quality assurance/control QA/QC of data to ensure maximum quality. Bias by time period and by other confounders such as HIV, gender and age, will be controlled for in the analysis. No historical data will be generated for cohort 2, as no routine data on HR-TB is available.

6.3. Participant Inclusion Criteria for cohorts 1 and 2

1. Ambulant adults ≥ 18 years of age
2. Newly diagnosed PTB patients receiving less than 5 days of treatment since new diagnosis:
   a) Cohort 1: < 5 days of DR-TB treatment
   b) Cohort 2: < 5 days of INH mono-resistant TB treatment preceding study entry for the current TB episode, or
3. Sputum positive (smear and or culture) TB patients classified as failing first line treatment
4. Any currently available Nucleic Acid Amplification Tests for drug-resistance detection changes/assay positive for M.tb infection with:
   Cohort 1: at least Rifampicin resistance

Cohort 2: Rifampicin susceptible co-occurring with INH, fluoroquinolone, ethionamide or aminoglycoside resistance (detected by Xpert XDR) occurring alone or in combination

5. Capacity to provide informed consent
6. HIV infected and uninfected participants are allowed in the study. Participants already on ART will be allowed in the study provided the ART regimen in use has no contraindications to the proposed TB drug regimen
7. Willing to have samples collected, stored indefinitely, and used for research purposes
8. Able to provide reasonable proof of identity (to satisfaction of study team member) at or prior to enrolment

6.4. Participant Exclusion Criteria

Study participants will be excluded if one or more of the following conditions apply:

1. Has a known severe allergy to any of the BPaL component drugs
2. Has DST showing infection with a strain resistant to any of the component drugs
3. Has TB meningitis, other central nervous system TB, or TB osteomyelitis; or
4. Is pregnant or breastfeeding
5. Is unable to take oral medications
6. Persons with any other medical condition, precluding study participation based on investigator judgement
7. Any co-existing condition that in the opinion of the attending clinician renders the participant unsuitable for participation in the study
8. Co-enrolment in other interventional research studies

6.5. Late Exclusion Criteria

1. Resistance to BPaL component drugs on pDST conducted post study enrolment

6.6. Screening Procedures

Two screening strategies will be adopted:

a) Patients with suspected pulmonary TB or confirmed *M.tb* positive (< 5 days since treatment initiation) will be screened and consented to provide an additional sputum sample for Xpert MTB/XDR testing *if required*. This will be *based on* the routine sample collected for any currently available Nucleic Acid Amplification Tests for drug-resistance detection changes
b) We will concurrently contact all patients with newly identified RR-TB during the study enrolment period directly for participation in this study (laboratory records)

The site investigator (or designate) will assess eligibility and ensure that the participant meets study inclusion criteria. Xpert MTB/XDR (Cepheid) will be implemented as an additional DR-TB screening test. All participants must test positive for *M.tb* and participants with RR-TB will be screened for additional resistance and enrolled in Cohort 1 (estimated n=880) while those without RR will be screened for isoniazid resistance and enrolled in Cohort 2. Participants with HR-TB will be enrolled in Cohort 2 (estimated n=400). As this is an operational study, accrual

into the study will be within a specified time frame. Overview of screening and enrolment approach is outlined in figure 3.

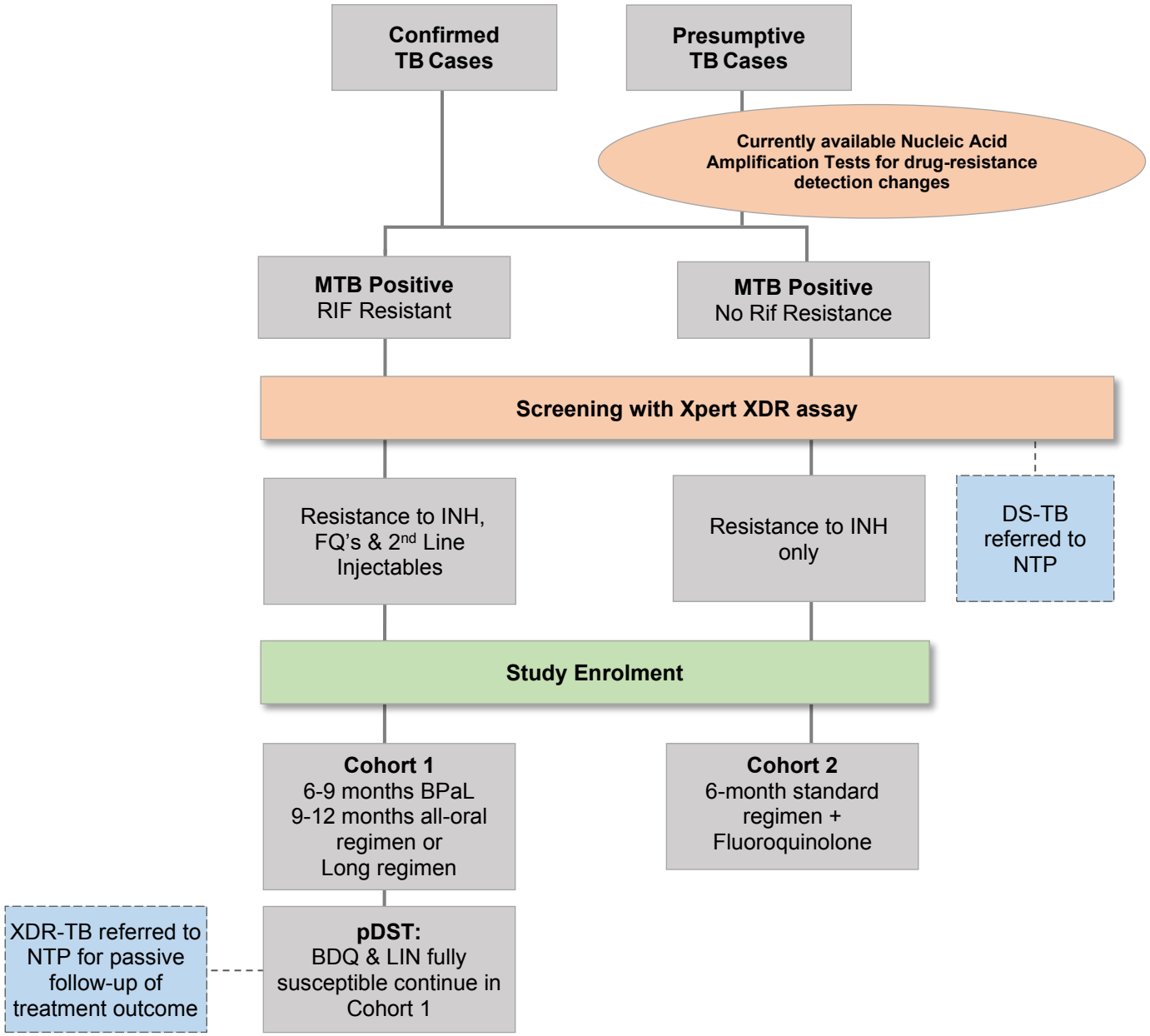


Figure 3: Study screening and enrolment for the TRiAD Study

6.7. Enrolment Procedures

Study staff will contact potential participants meeting eligibility criteria, based on the Xpert XDR test, for study enrolment. Participants will be re-assessed for their willingness to participate in the study. Participant accrual at all sites will occur over 12 -18 months from the date of enrolment of the first participant.

Participants will be given further information about the study. Ineligible participants will be referred to the National Tuberculosis Programme (NTP) for further management. Eligible

participants who agree to study participation will undergo study informed consent procedures (signature or give a thumb print in the presence of a witness if illiterate). Enrolled participants will be given a signed copy to take home.

After obtaining study informed consent, clinical research sites will:

- Obtain consent from participants for sputum sample storage and further analysis
- Record participant contact information including physical address
- Interview participants to obtain demographic details, medical history (including all prior TB diagnoses, history of previous TB drug intake
- Conduct a targeted clinical examination

7. STUDY ASSESSMENTS AND FOLLOW-UP

7.1. Schedule of evaluations

The sequence of study visits and procedure schedules are presented in tables 3 and 4 schedule of evaluations for cohort 1 and 2, respectively. These tables detail visit requirements for each in-person follow-up visit. Each follow-up visit will include collection of a sputum sample, a clinical examination and assessment for adverse drug reactions. Study staff will be trained to conduct study procedures in a standardised manner. Study specific standard operating procedures (SOPs) will guide this process.

Screening (Cohorts 1 and 2):
Screening will include the provision of introductory study information, assessment of eligibility criteria and obtaining written informed consent for screening procedures. Participants who meet the eligibility criteria will provide *up to* two sputum samples for currently available Nucleic Acid Amplification Tests for drug-resistance detection and Xpert XDR testing. For potential participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.

Evaluations for Cohort 1:
Participants will be scheduled to undergo appropriate evaluation at baseline, during and after treatment. Study visits will occur at week 2, monthly for the duration of DR-TB treatment and 3-monthly following completion of treatment where allowable within the study's operational time frame. Participants on short-regimen will be seen for a maximum of 3 post-TB treatment visits, 3 months apart (Table 3). Active follow-up will occur for the duration of TB treatment and passively thereafter, for a maximum of 18 months after study enrolment. Participants who receive long treatment regimens will be actively followed-up for the duration of the intensive phase of treatment and passively thereafter to obtain an end-of-treatment outcome. Research-specific activities during follow-up include assessment of clinical and microbiological response to treatment, solicitation and reporting of adverse events and serious adverse events, administration of study specific questionnaires related to costs, acceptability and feasibility of the intervention. Passive follow-up will be conducted telephonically or through NTP registers to assess rates of relapse after TB treatment completion. Study related specimen collection will occur at baseline (enrolment) and at all follow-up visits. Baseline sputum samples will be collected for Xpert MTB/XDR testing, pDST, WGS, and TB-MBLA testing. Follow-up sputum samples will be collected for routine culture and susceptibility testing and sputum storage for batched TB-MBLA testing.

Evaluations for Cohort 2:

Participants will be referred to the NTP and will not undergo further active follow-up within the study (table 4). Treatment outcomes for these participants will be monitored passively through monthly telephonic monitoring or through routinely collected outcome data within the national TB program until 15 months after enrolment.

Table 3: Schedule of Evaluation for Drug-Resistant Tuberculosis participants in the TRiAD Study Cohort 1

Visit	**Screening**	**Enrolment**		**Treatment and Follow Up Period [a]**										
Time of visit			24h after 1st treatment dose	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 15	Month 18
Inclusion/Exclusion Criteria	X	X												
Informed Consent	X	X												
Storage informed consent [g]		X												
Sociodemographic Information		X												
Medical/treatment History [b]		X												
Clinical Exam [c]		X		X	X	X	X	X	X	X	X	X	X	
TB Symptom Profile	X	X		X	X	X	X	X	X	X	X	X	X	
Peripheral Neuropathy Assessment		X		X	X	X	X	X	X	X	X	X*	X	
ECG monitoring		X		X	X	X	X	X	X	X	X	X	X	
Chest X-Ray [d]		X						X		X				
Laboratory Safety Assessments [e]		X		X	X	X	X	X	X	X	X	X	X	
Sputum Sampling [f]	X	X		X	X	X	X	X	X	X	X	X	X	
Blood sampling (1x4ml EDTA Tube) [h]		X					X						X	

Spot Urine collection sample (approximately 30ml) [i]		X												
Self -collection urine sample (approximately 5L) [j]			X							X				
Participant Questionnaire [k]		X												
Solicited Adverse Events (AES) /SAE [l]				X	X	X	X	X	X	X	X			

Notes:

a. **Treatment and follow-up:** Active follow-up will occur during TB treatment only, passive follow-up visits up to 18 months post-TB treatment, no specimen collection during passive follow-up. Visits for month 12 onwards applicable to participants who continue treatment for longer than 6 months only. Passive follow-up visits will collect AE's, SAE's, verification of survival and participant reported TB outcome information. These will be conducted telephonically

b. **Medical History:** will include TB treatment history, HIV/Status and CD4 and Viral load Monitoring: If HIV status is unknown or reported negative in the absence of documentation, HIV test should be requested. CD4 and Viral load test to be conducted for all HIV-positive participants as per standard of care

c. **Clinical Exam:** will include random blood glucose test, ophthalmic examination of visual acuity and colour vision assessment, pregnancy test will be conducted in women of child-bearing potential and peripheral neuropathy assessment

d. **Chest X-Ray:** Will be conducted at screening visit, month 4 (South African standard of care) and thereafter at the request of the treating clinician if deemed necessary. In Nigeria, X-rays will be done at screening visit, month 4 and end of treatment

e. **Laboratory Safety Assessments:** Haematology, full blood count, clinical chemistry and urinalysis - as per routine in-country standard of care

f. **Sputum Sampling:** *1* sample will be collected at baseline/screening: for currently available Nucleic Acid Amplification Tests for drug-resistance detection, routine culture and Xpert XDR testing, *an additional sample will be requested if required,* 2 samples will be collected at enrolment: storage for TB-MBLA and WGS/MIC testing

g. Optional Storage Consent for additional sampling collection and storage: Subset of participants who are willing to consent to provision of urine and blood samples at enrolment, month 3, the end of TB treatment, and 6 months post treatment completion if still in follow up, will be required to provide written consent

h. **Optional Blood Sampling: #** Subset of participants to provide samples to be collected at enrolment, month 3, at the end of TB treatment, and 6 months post treatment completion if participant still in follow up
i. **Optional Spot Urine Collection Sample: Subset of participants to provide** pre-treatment spot urine collection to be conducted during the enrolment visit
j. **Optional Self-collection of Urine Sample: Subset of** participants to collect a 24-hour urine sample following first dose of TB treatment and another 24-hour self-collection urine sample at month 6 after treatment initiation
k. **Participant Questionnaire:** assess participant associated costs and acceptability of study approach; schedule for administration to be finalised with sub-study protocol
    l. **Reporting of adverse events:** record solicited grade 3 and 4 adverse events during treatment phase only and all serious adverse events throughout study follow-up.

Table 4 : Schedule of Evaluation for Drug-Resistant Tuberculosis participants in the TRiAD Study Cohort 2

Visit	Screening	Enrolment	Treatment and Follow Up Period [a]									
Time of visit			Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 15
Inclusion/Exclusion Criteria	X	X										
Informed Consent	X	X										
Sociodemographic Information		X										
Medical/treatment History		X										
Clinical Exam		X										
TB Symptom Profile		X										
ECG monitoring		X										
Chest X-Ray [b]		X										
Sputum Sampling [c]	X	X										
Telephonic Assessment			X	X	X	X	X	X	X	X	X	X

Notes:

a. **Treatment and follow-up:** Passive follow-up visits up to 6 months post-TB treatment, routine monitoring of treatment response. Passive follow-up visits will collect AE's, SAE's, verification of survival and participant reported TB outcome information. These will be conducted telephonically

b. **Chest X-Ray:** Will be conducted at screening visit, and thereafter at the request of the treating clinician if deemed necessary. In Nigeria, X-rays will be done at screening visit, month 4 and end of treatment

c. **Sputum Sampling:** 1 sample will be collected at baseline/screening: for any currently available Nucleic Acid Amplification Tests for drug-resistance detectionand Xpert XDR testing, an additional sample will be collected if required.
1 sample will be collected at enrolment: for culture and storage for WGS/MIC testing

The study SoE will be followed except when procedures are clinically indicated or not in accordance with clinical judgement.

7.2. General Mycobacteriology

The following bacteriological tests will be performed at the local reference laboratory as per standard practice: smear, culture, diagnostic LPAs and pDST to BDQ and LZD in pre-XDR TB participants. At each visit, one early morning sputum sample will be tested for acid-fast bacilli (AFB) smear and culture. Study specific procedures assays will be carried out according to procedures described in the study laboratory manual. Sub-cultures will be shipped to Tuberculosis Supranational Reference Laboratory, San Raffaele Scientific Institute (OSR) for specialized tests such as MIC and WGS.

Table 5: Overview of microbiologic assessments performed after each visit

Visit	Sample Type	Microbiologic Assessments	
		Routine Testing	Study Intervention
Screening	< 2x Sputum samples	• Direct microscopy for AFB; currently available Nucleic Acid Amplification Tests for drug-resistance detection changes, Hain Assay MTBDR*plus* and MTBDR*sl* • Culture for the presence/absence of *M.tb* • Phenotypic DST to bedaquiline and linezolid	• GeneXpert XDR test[1]
Enrolment	Sputum X2		• Culture for presence/absence of *M.tb* • Sub-culture for storage and shipment for MIC and WGS[3] • Sputum collection for TB-MBLA processing [2]
All visits post screening	Sputum X2	• Culture for the presence/absence of *M.tb*	• Sputum collection for TB-MBLA processing [2] • Any culture positive sample obtained during or after treatment will be stored at site level (*optional*)

Notes:

[1]**Xpert XDR testing:** will be conducted on sputum sample collected at the screening visit following initial TB diagnosis by currently available Nucleic Acid Amplification Tests for drug-resistance detection changes. The Xpert MTB/XDR assay will be conducted in real-time to evaluate INH and second-line resistance and recommend the appropriate treatment regimen. This test will be conducted once off at the initial visit.

[2]**TB-MBLA testing:** the test will be conducted on stored sputum samples. The test will be conducted using LifeArc TB-MBLA test kits. This assay will be conducted to assess the clinical utility of the assay, not for clinical management. It is a reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay that uses 16S-rRNA as a marker to detect and quantify the load of viable *M.tb* bacteria in a participant's sputum sample. The process starts with RNA isolation from *M.tb* bacteria, followed by RT-qPCR to quantify the RNA, then conversion of the RT-qPCR output (cycle threshold [CT] values) into bacterial load values (estimated colony forming units per millilitre [eCFU/ml]) using a standard curve.

[3]**Culture for storage, MIC and WGS:** Isolates will be cultured from sputum samples collected at the screening/enrolment visit using the BD BACTEC MGIT 960 culture system at National Reference TB Laboratory. Cultured isolates will be stored at -80 degrees Celsius for further processing. 70% of clinical isolates will be sent to the study reference laboratory; OSR. OSR will perform quality assurance assessments of the Xpert MTB/XDR cartridge to be tested. The drug patterns of resistant strains detected with the XDR assay will be fully characterized by OSR. In parallel, OSR will populate and develop a catalogue of resistance of the sites, complemented by MIC testing, and seek to identify resistance markers to guide future diagnosis and treatment decisions. WGS testing will be conducted on 70% of total samples from participants with RR-TB and HR-TB enrolled from all sites in cohort 1 and 2, respectively. MIC testing for full phenotypic DST will be prioritized on a subset of 480 samples maximum, including strains with unknown mutation patterns and/or from participants failing the proposed regimen. The accuracy of Xpert MTB/XDR test results for drug resistance prediction will be assessed and quality controlled by WGS analysis. One aliquot of viable isolates from study samples will be referred from sites to OSR, arranging one shipment in year 1 and two shipments per year in the years 2, 3, 4.

7.3. Cost effectiveness and acceptability analysis

7.3.1 Cost effectiveness

Through cost-effectiveness analyses we will determine the incremental cost per DALY averted from combined currently available Nucleic Acid Amplification Tests for drug-resistance detection and Xpert/XDR implementation, followed by an all-oral, shorter treatment regimen compared to the conventional standard of care for both DR-TB patients. Cost data on diagnostic and treatment algorithms will be collected through an ingredient approach from a societal perspective, including both health system and patient costs. Both provider and patient cost data will be collected empirically from all nine sites once the optimal implementation scenarios have been generated. Gaps in provider costs captured in precious costing studies will be collected through semi-structured interviews of key informants and document review. Patient costs of cohorts 1 and 2 participants will be collected via questionnaire by trained data collectors in tandem with select parent study follow-up visits.

The primary outputs will include incremental cost per DALY averted and incremental cost per day of treatment delay averted compared with historical controls. These outcomes are assessed from the societal perspective and reported from each of the societal, provider, and patient perspectives. The cost-effectiveness comparison between the intervention and the standard of care will be modelled using primary data from the parent study, primary cost data

from providers and patients from all five trial sites, secondary data concerning national population characteristics and standard of care outcomes, as well as expert opinion, where necessary. The time frame of the model-based analysis will be from initial diagnosis to end of life. Deterministic and probabilistic sensitivity analyses will be conducted on model parameters and methodological assumptions.

7.3.2 Acceptability analysis

In order to assess the acceptability and feasibility of implementation of the newly proposed triaging and treatment algorithms we will adopt a mixed methods study design. Quantitative data will be collected through pre-structured questionnaires, while in-depth interviews will also be conducted to complement and illustrate the quantitative study results. We will recruit participants, and health care workers (HCW's) from each participating sites (5 in Ethiopia, 2 in Nigeria, 2 in South Africa) as well as relevant policy makers from each country. For the collection of quantitative data, per site, we will interview at least 10-25 participants (50 per country), 7-15 HCWs depending on the number of HCW's directly involved in the implementation and execution of the intervention, approximately 35 per country, and at least 3 policy makers (one at national, one at provincial and one at district level (i.e., programmatic management of DR-TB [PMDT] focal persons in each country). For the qualitative data collection, we will continue data collection until data saturation has been reached, although this will not be feasible for the policy makers, as there is only one to be interviewed per level. We will purposively and concurrently sample interviewees to include maximum variability: men and women from different participating sites, participants assigned to different regimens with or without comorbidities, fully or partly adherent to therapy, HCWs and stakeholders with different job description and years of experience in the setting.

We will train local interviewers (one per participating site) on the topic guide, interview competences, and obtaining informed consent. The trained interviewer will conduct interviews using the pre-structured questionnaires and semi-structured in-depth individual interviews. Interviewers will be supervised by a local focal person with background in qualitative research, who will also oversee interview activities, and data collection (including quality and data saturation) and storage. All communication during interviews will be in the local language. We will obtain a-priori written informed consent for audiotaping the in-depth interviews and publication of anonymized results. Following each in-depth interview, the interviewer will describe interview setting, including ambiance and emotions, and verbatim transcribe and translate audio-recorded interviews in English. Interviewees will receive a small incentive for the time spent on the interview.

Analysis of the quantitative data will be done using statistical software (Stata or SPSS). Proportions and median/mean values will be calculated as appropriate. Differences between subgroups will be analysed. For the qualitative part, after familiarization with the data, two researchers will analyse data (QSR Nvivo10 software) by using an applied thematic approach, which allows for inductive coding and thematising. After development of a coding scheme, which will be refined along the coding process, two researchers and an independent reviewer (one from each participating site) will regularly discuss interpretation of data, coding, and emerging (sub)themes. Additional to overarching study results, we will stratify analysis per country, health care worker/participant perspective, gender, and type of regimen received. We

will present study results by themes, including relevant interviewee quotes. This exercise will be conducted after each interview to judge if new themes arise from the interview. If no new themes arose, data saturation was reached and no more in-depth interviews will be conducted for that specific group of participants. We define acceptability as a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. Both persons receiving (participants) and delivering (health care workers (HCW) and policy makers) the intervention will be included in the assessment. Feasibility reflects how viable implementation of the intervention is. Both the (anticipated and experienced) acceptability and feasibility will affect the intervention's uptake and effectiveness.

8. TREATMENT CONSIDERATIONS

8.1. Interruptions to treatment

The study treatment regimen may be interrupted at the discretion of the local PI for:

- A serious adverse event
- The investigator decides to withhold treatment in the interest of the safety and well-being of the participant
- Lack of effectiveness

If treatment is interrupted for a suspected serious drug reaction, attempts should be made to identify the drug concerned. After resolution of the suspected adverse reaction, treatment may be gradually re-introduced until the allocated regimen has been re-instituted.

In the case of the BPaL regimen, if treatment is interrupted for more than 35 consecutive days, the participant will be referred to the assigned expert TB clinical committee to decide on further management including need for change to a new individual regimen, based on clinical assessment and reason for interruption. Any missed doses should be made up at the end of the treatment to complete 24 weeks of therapy. Missed doses of linezolid alone due to adverse reactions are not to be made up at the end of treatment. Reasons for missing treatment must be identified and addressed early and noted in the participant's file for analysis for factors associated with (lack of) treatment success (33).

In the event that the local PI considers that treatment needs to be modified or changed, he or she should inform the coordinating centre by submission of an SAE form and discuss treatment plans with a member of the study medical monitoring team (MMT).

8.2. Discontinuation of treatment due to toxicity or treatment failure

The study regimens will be discontinued in some participants. In such cases, participants will be evaluated by the MMT and switched to an individualized regimen, based on the WHO guidelines for regimen design. The most common situations in which the regimen may be discontinued include:

- **Intolerable severe toxicity**. One or more drugs may need to be suspended permanently due to severe toxicity. In such cases, the clinical committee should review the medical history carefully to determine how the regimen should be modified (see discontinuation/modification criterion below).
- **Treatment failure**. If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated if culture is still positive at month 4, whether or not the regimen is changed, in order to inform future management decisions.
- **Resistance to drugs in the regimen**. For participants who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to component drugs is discovered after treatment is initiated, it may be necessary to modify, extend treatment duration or discontinue the regimen.
- **Pregnancy during treatment**. For participants who become pregnant during treatment, it may be advisable to modify or discontinue novel regimens. A decision regarding continuation or discontinuation of the regimen should be made after a review by the study MMT and discussion with the participant

For participants discontinued from study treatment or whose treatment is changed and participants referred to the NTP, every effort should be made to continue passive follow up (at a reduced frequency if necessary), unless the participant has specifically withdrawn consent for further follow-up. In this event, a final status form should be completed. Details for management these participants will be outlined in a study specific SOP.

8.3. Interruptions to care

8.3.1. Missed Visits

For each participant, clinic staff will obtain or confirm contact information. In the event that a participant misses a scheduled appointment, staff will try within the week following the missed appointment to establish telephonic communication with the participant and/or treatment supervisor through all possible means which they have approved while protecting their confidentiality. Permission for this contact must be obtained in the initial consent form. All attempts to locate a participant following each missed appointment will be documented in the source document. The need to attend all scheduled follow-up visits will be emphasized to all study participants at every visit. Every site will develop its own method for tracing and retaining participants in the study.

Participants who miss their scheduled appointment will be contacted and arrangements made for a new appointment. If participants are not successfully reached by phone/text messaging, a home visit will be arranged to ensure contact. Participants returning after missed appointments will have procedures for the visit closest to their total time in follow up performed. Subsequent visits will continue as scheduled. However, treatment to be prescribed should be determined by the actual number of days already taken and not by time in the study.

A participant will be deemed to be missing if he/she does not attend the treatment centre to take the treatment as prescribed for a period of one week. If the participant has not resumed

treatment within seven days, i.e., the participant has missed at least two weeks of treatment; a note should be made in their clinic notes with details of attempts to contact the participant.

8.3.2. Loss to follow-up

Every effort will be made to keep participants engaged in follow-up. If the participant does not return to the clinic before the study is closed, the final form will be completed at the time of study closeout. The form should indicate that the participant was lost to follow-up. The "loss to follow-up" designation cannot be made for any participant until at least 3 months after the participant's scheduled visit.

9. STATISTICAL CONSIDERATIONS

9.1. Power and Sample size calculations:

The study will be powered based on the two primary endpoints:

i) Numbers needed to detect a reduced time to resistance-pattern appropriate treatment initiation for all drug-resistant cases compared to the historical cohort; and

ii) The difference in proportion of favourable treatment outcomes compared to the historical cohort, allowing for stratification by study site (geographical location).

Current data, mainly from South Africa, show a median time to resistance-pattern appropriate treatment initiation for drug-resistant participants between 15 and 46 days (1-3). With an assumption of an anticipated time to treatment initiation of one week in our study (allowing time for providing repeat sputum samples and delays in Xpert testing), 220 RR-TB participants must be enrolled in cohort one in each country (440 in South Africa), to achieve 90% power to show a shortening of time to treatment initiation. This sample size includes an allowance for an overall 15% loss to follow-up.

Table 6: Reported median times (in days [IQR]) to treatment of drug-resistant TB in literature

Patient type		**Xpert-based**	**LPA-based**	**Phenotypic DST-based**	**Location/date**	**Ref**
All	MDR+XDR	17 *[9-47]*	38 *[23-54]*	81 *(49-115]*	Johannesburg, South Africa 2017	(34)
	RR	0 *[0-1]*	20 *[10-16]*	106 *[30-124]*	Multi-site 2011 (Boehme)	
	MDR	8 *[5-25]*	50		MSF Cape Town 2015	(35)
	MDR	17 *[13-22]*	43 *[40-46]*		Cape Town 2014	(36)
	MDR	15 *[1-29]*	32 *[7-57]*		South Africa 2017	(37)

	RR (only 4 pts)	2	21	40 (MGIT)	Cape Town South Africa 2011	
	MDR			88 *[29-126]*	Korea 2019	(38)
	XDR			97 *[79-126]*	Korea 2019	(38)
Smear positive	MDR + XDR	15 *[1-42]*	32 *[7-42]*	81 *[75-107]*	Johannesburg, South Africa 2017	
Smear negative	MDR + XDR	-	54 *[45-62]*	Johannesburg, South Africa	Johannesburg, South Africa 2017	

For the proportion of favourable study outcomes, we used the most recent treatment completion proportions of Kwazulu-Natal province of South Africa, including one of the study sites (4). The average MDR-TB treatment completion proportion is 63%, varying from 57% in their long regimen to 74% using a bedaquiline-based short regimen. The study sample size of n=220 per study site as calculated above will be sufficient to detect an improvement in treatment outcomes with a minimum difference from 74% to 85% (80% power; larger differences with 90% power [from baseline success of 71% and less]), also allowing for 15% loss to follow-up.

The estimated XDR prevalence among MDR cases is 4.3% in South Africa (2018 Global TB report), 0.6% and 0.7% in Nigeria and Ethiopia (2019 Global TB report). This would mean that N=880*4.3% = 38 XDR cases. As BPaL eligibility extends to pre-XDR patients and treatment intolerant MDR patients, it is expected that a higher number will be on BPaL. A total of 40 participants (including 15% LFU) are needed to detect an improvement from 53% to 85%. This number should be possible for all sites together. Assuming approx. 10% HR-TB in each site, we aim to enrol N=400 in cohort 2 which would allow for approximately 100 HR-TB participants per site, which should be sufficient for studying associated secondary study outcomes.

9.2. Analysis including statistical methods:

Primary endpoint analysis:

- The time to appropriate treatment initiation will be calculated as median days (with interquartile range) between the first sputum collection date and the date of start of the regimen appropriate to the drug resistance pattern (defined as drug-resistance pattern appropriate treatment). This will be compared to the same time in the historical cohort and stratified by geographical location (study site). Confounding will be addressed by multivariable analysis.
- The proportion of favourable study outcomes [treatment cure or completion, based on the WHO definitions (5) will be calculated in the overall study population of cohort 1, and compared with the same proportion in the historical cohort, and stratified by geographical location (study site). In a secondary analysis, these proportions will also be calculated per type of DR-TB. Confounding will be addressed by multivariable analysis.

Both of these outcomes will only be calculated in the primary cohort (cohort 1), as no reliable historical data exist for either endpoint for HR-TB (cohort 2).

Secondary endpoint analysis:

- Prevalence of HR-TB stratified by geographical location. This will be calculated in cohort 2 and stratified by HIV status.
- The incidence of adverse events will be divided into adverse events and serious adverse events and calculated in proportions using both cohort 1 and 2. These will also be stratified by type of DR-TB, treatment regimen, and HIV status.
- Feasibility and acceptability (participant and health care provider perspective), stratified by type of DR-TB regimen (cohort 1 and 2)
- Cost-effectiveness (cost per person tested and incremental cost per DR-TB participant timely initiated on the resistance pattern-appropriate regimen) and, following from that, optimal placement of Xpert XDR in diagnostic & treatment algorithm (cohort 1 and 2)
- Accuracy of Xpert XDR testing (in comparison with culture + DST/LPA/Next-generation sequencing [NGS]), by type of DR-TB (cohort 1 and 2)
- Operational feasibility of Xpert XDR testing (infrastructure requirements and HR needs) (cohort 1 and 2)
- Quality of Xpert XDR tests (indeterminate rate, DNA contamination rate, and performance variation [in time and between sites]) (cohort 1 and 2)
- Clinical utility and feasibility of TB-MBLA in bacteriological follow-up of DR-TB (in comparison with routine culture), by type of DR-TB and regimen (cohort 1)
- Additional resistance to new and repurposed drugs, by type of DR-TB and regimen (cohort 1 and 2)
- Mathematical modelling of TB-MBLA trajectories in response to treatment

Timing of analysis:
The majority of the above outcomes will be analysed after the end of follow-up, however an interim analysis of the primary study outcomes as well as the safety outcomes is planned for Month 32 (M32) or after complete Month 12 follow-up (M12FU). This will allow for timely informing of policy makers as these new diagnostic tools and regimens are being rolled out.

9.3. Outcome Status

Outcomes are based on WHO's reporting framework for tuberculosis in 2020 (39).Treatment outcome definitions have recently been revised by WHO and will be updated in the 2021 revision of WHO's *Definitions and reporting framework for tuberculosis.* Once this guideline becomes available and the new definitions are adopted for programmatic implementation, the protocol will be updated (**https://www.who.int/publications/i/item/9789240022195**).

Table 7: Treatment outcomes for RR-TB/MDR-TB/XDR-TB participants treated

Outcome	Definitions per TRiAD Protocol	2021/2022 WHO Definitions
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase	A pulmonary patient with bacteriologically confirmed DR-TB at the beginning of treatment who completed the recommended treatment , with evidence of bacteriological response* and no evidence of failure
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase	A patient who completed treatment as recommended and who does not meet the definition of cure or treatment failure
Treatment failed *	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: - lack of conversion by the end of the intensive phase, or - bacteriological reversion in the continuation phase after conversion to negative, or - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or - adverse drug reactions (ADRs)	A patient whose treatment regimen needed to be terminated or permanently changed to new regimen or treatment strategy. Reasons for change include : - No clinical and or bacteriological response - Adverse drug reaction/s - Evidence of additional drug resistance to medicines in the regimen
Died	A participant who dies for any reason during the course of treatment.	A patient who died for any reason during treatment
Lost to follow-up	A participant whose treatment was interrupted for 2 consecutive months or more.	A patient with treatment interrupted for ≥2 consecutive months for any reason without medical approval
Not evaluated	A participant for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)	A patient recorded in the register and who does not have the necessary recorded data to enable classification of any outcome
Treatment success	The sum of cured and treatment completed	Is sum of cured and treatment completed

Sustained treatment success (optional outcome)		A patient assessed at 6 months and at 12 months after successful TB treatment, who is alive and free of TB.

*For treatment failed, lack of conversion by the end of the intensive phase implies that the participant does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for *Cured, Treatment completed* and *Treatment failed* start to apply.

The terms “conversion” and “reversion” of culture results are defined as follows:

- **Conversion** (to negative): culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion** (to positive): culture is considered to have reverted to positive when after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive.

“Recurrent TB” is defined as being either of the following circumstances after cure or completion of treatment:

- Two consecutive positive cultures, or
- One positive culture with clinical signs and symptoms or radiographic deterioration (an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB).

If genotyping is available, recurrent TB may be further classified as relapse, reinfection, or undetermined as defined below:

- **Relapse**: isolates of the recurrent episode share the same genotype pattern with isolates of the first episode of MDR-TB.
- **Reinfection**: isolates of the recurrent episode and isolates of the first episode of MDR-TB have different genotype patterns.
- **Undetermined:** there is insufficient information to determine whether the recurrent episode is due to relapse or reinfection.

10. PROCEDURES FOR ASSESSING SAFETY AND ADVERSE EVENT REPORTING

10.1. Adverse Events (AEs) and Adverse Event Reporting

An AE is defined as any untoward medical or social occurrence in a clinical research participant that may or may not have a causal relationship with the study drugs/interventions. The principles of ICH GCP require that investigators follow specific procedures when notifying adverse events or reactions in clinical trials.

Adverse drug reaction (ADR): is defined as a response to a medicine in humans that is noxious and unintended, including lack of efficacy, and that occurs at doses normally used in man and that can also result from overdose, misuse or abuse of a medicine. All adverse events judged by either the investigator as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. ADRs that occur following enrolment will be considered AEs and will be recorded on the AE CRF.

Unexpected Adverse Reaction (UAR): is a reaction in which the nature, specificity, severity and outcome is not consistent with the approved package insert for a registered medicine (or investigator's brochure for an investigational product). When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected**.** UARs that occur following enrolment will be considered AEs and will be recorded on the AE CRF.

Clinical AEs grade 3-5 will be recorded via the AE recording CRF. The clinical course of each grade 3 and 4 event should be followed until resolution, stabilization, or until it has been determined that the study treatment is not the cause. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline/non-gradable range). AEs that are ongoing at the time of study exit will be followed up for up to 30 days after study exit and then, if not resolved, will be referred to a health care provider for further follow-up.

The Principal Investigator (PI) or designee must determine the severity of the AE and document it on the appropriate CRF (AE Form). Generally if toxicity occurs on any of the drugs used in the study, the decision on whether to continue or stop the drug will depend on severity of the toxicity, duration of treatment received, whether the participant has culture converted, how many other active drugs are in regimen, how essential the drug is to the regimen and whether it can be replaced with another active drug. Each decision will be decided upon by the attending clinician. Severity does not have the same meaning as seriousness, since a participant can experience a severe event such as a skin rash that is not serious. Grading is subjective, based upon perspective of the attending clinician and participant. Additionally, especially for measurements and laboratory results, grading may differ according to age, gender, body mass index (BMI) and weight.

Table 8: Grading the severity of ADR; following common guidelines and management for the treatment of TB used in the TRiAD study

Grade	Severity Rating	Definition
Grade 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required. The participant will be followed carefully and the study drugs will be continued
Grade 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required. The participant will be followed more closely, with additional laboratory and/or clinic visits as necessary; treatment should be continued unless in the view of the clinician/investigator this would be unsafe.

Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
Grade 4	Potentially life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.
Grade 5	Fatal	Death

An AE **does not** include:

- Pre-existing diseases or conditions present or detected prior to start of study drug administration that does not increase in grade. All pre-existing conditions (grade 3 or higher) must be clearly documented on the enrolment CRF If the frequency, intensity, or the character of the condition worsens to grade ≥3 level during the reporting period, the event should be defined as an AE;
- Medical or surgical procedures (e.g. Surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Situations where an untoward medical occurrence has not occurred (e.g. Hospitalization for elective surgery, social and/or convenience admissions).

The PI or designee must determine the relationship of the AE to the drugs under investigation and document on the appropriate CRF (AE Form). For each AE, an assessment of the relatedness to the study drug will be made using the WHO criteria:

Probable: The event is an identifiable clinical or laboratory-linked phenomenon; the time elapsed between the administration of the drug and the occurrence of the event is plausible; the event cannot be explained by concurrent disease or any other drug or chemical; the participant recovered within a plausible length of time following withdrawal of the drug; re-challenge did not occur, or the result is unknown.

Possible: The time elapsed between the administration of the drug and the occurrence of the event is plausible; the outcome of withdrawal of the suspect medicine is not known, and/or the medicine might have been continued and the final outcome is not known; and/or there might be no information on withdrawal of the medicine; and/or the event could be explained by concomitant disease or use of other drugs or chemicals; and/or there might be no information on the presence or absence of other medicines.

Unrelated (Unlikely): The event occurred with a duration to onset that makes a causal effect improbable with the drug being considered; and/or the event commenced before the first administration of the drug; and/or the drug was withdrawn and this made no difference to the event when, clinically, recovery would be expected; and/or it is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved. This category has also been referred to as doubtful.

All AEs will be captured regardless of the association or otherwise to the study product and reported on the AE CRF in accordance with study specific procedures. All AE reports will contain at least the date the AE occurred, a brief description of the event, the relationship to

study drug, the study drug action taken, the outcome, date resolved, and the seriousness of the event.

10.2. Expected Disease Related Events

In this study population, with DR-TB and HIV, some participants may be critically ill and will have a complicated clinical course. Opportunistic infections and/or nosocomial infections are expected. Disease-related events may be frequent and include:

- Death which will always be reported as an SAE
- HIV-related opportunistic infections / illnesses
- Common ART side-effects e.g. anaemia, sleep disturbance, diarrhoea, mild renal dysfunction
- Hospitalisation due to respiratory symptoms or HIV related conditions

Expected disease-related events will be recorded in study CRFs but will not require reporting to regulatory authorities unless the severity of the event was considered to be unexpected.

10.3. Serious Adverse Event Reporting

An SAE or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) includes an experience where any AE, AR or UAR that at any dose:

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity; or is a medically significant/ important event or reaction that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

All serious ADRs will be reported.

10.4. Anti-TB Drug Information for new study drugs

There are no absolute contraindications for the use of any drug in the treatment of DR-TB, a disease that poses serious risk of death or debilitation to the participant if treated inadequately. However, relative contraindications, side-effect profiles and drug-drug interactions must be considered when selecting and administering the drug throughout. If the clinician judges that the potential benefits outweigh the potential risk (also considering alternative treatment options) treatment may proceed with caution. The Companion Handbook to the WHO guidelines for programmatic management of drug-resistant tuberculosis (40) provides relevant information for most anti-TB medicines, with the exception of pretomanid which was in use when the handbook was written. Details for key drugs in the TRiAD study are summarised in Table 9 below and guidelines for medical management can be found in Appendix I. Wherever necessary, advice may be sought from the study MMT.

Table 9: Summary profile of drugs to be used for treatment of DR-TB in the TRiAD study

Bedaquiline	
Activity against TB, Mechanism of action, and metabolism	Bactericidal: Inhibits ATP synthesis. The drug has a 5.5-month half-life. Cytochrome P450 3A4 (CYP3A4) is the major CYP isoenzyme involved in the metabolism of bedaquiline. The metabolism leads to the formation of an M2 metabolite which is not thought to contribute significantly to clinical efficacy but may contribute to QTc prolongation. Bedaquiline is mainly eliminated in faeces. The renal clearance of unchanged drug is insignificant.
Dose	Adults: 400 mg once daily for 2 weeks, followed by 200 mg, 3 times per week for 22 weeks with food. If a dose is missed during the first 2 weeks of treatment, participants should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, participants should take the missed dose as soon as possible, and then resume the 3 times a week regimen.
Special Circumstances	Use in renal disease: No dosage adjustment is required in participants with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution). Use in hepatic disease: No dosage adjustment is required in participants with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks. Use in pregnancy/breast feeding: Very limited data. Each case must be individually assessed.
Adverse Reactions*	Common: Nausea, vomiting, abdominal pain, loss of appetite, joint pain (arthralgia), headache, chest pain, haemoptysis Serious: QT prolongation (more common in hypokalaemia, proarrhythmic conditions, of if combined with other QTc-prolonging drugs), hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases. Possibly an increased risk of pancreatitis.
Contraindications	Do not use or discontinue bedaquiline if: • Clinically significant ventricular arrhythmia. • A QTcF interval of >500ms (confirmed by repeat ECG). • Severe liver disease. Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit): • Use with other QT prolonging drugs (see drug interactions) • A history of torsade de pointes • A history of congenital long QT syndrome • A history of hypothyroidism and bradyarrhythmias • A history of uncompensated heart failure

	• Serum calcium, magnesium or potassium levels below the lower limits of normal. Any syncopal event (e.g. fainting) should prompt immediate medical evaluation and ECG.
Drug Interactions*	Anti-arhythmic drugs, tricyclic anti-depressants, anti-psychotics, chloroquine & hydroxychloroquine, some other TB drugs (e.g. clofazimine & fluoroquinolones), and macrolide antibiotics may increase risk of QTc prolongation. CYP3A4 inducers (including rifampicin, rifabutin, rifapentine, phenytoin and carbamazepine) can accelerate metabolism of bedaquiline resulting in reduced effect. CYP3A4 inhibitors (including azole antifungals) slow metabolism of bedaquiline resulting in increased concentrations of bedaquiline. Some anti-retroviral drugs are CYP3A4 inducers (e.g. efavirenz) or inhibitors (e.g. the protease inhibitors), so combined HIV and TB therapy requires careful consideration.
Guidance on monitoring	ECG: before initiation of treatment, and at least 2, 4, 8, 12 and 24 weeks after starting treatment. More frequently if heart conditions, hypothyroidism or electrolyte disturbances are present. LFT: at baseline and repeated monthly.
Pretomanid	
Activity against TB	Indicated as part of a combination regimen with bedaquiline and linezolid for treatment of adults with pulmonary XDR or treatment-intolerant or nonresponsive MDR TB
Dose	Pretomanid 200 mg daily 26 weeks
Special Circumstances	Use in renal or hepatic disease: Effect on the safety, effectiveness, and pharmacokinetics unknown. If hepatotoxicity develops on a pretomanid-containing regimen, the entire regimen should be interrupted if: • Any aminotransferase elevation is accompanied by a total bilirubin elevation >2x ULN • Aminotransferase elevations are >8 x ULN • Aminotransferase elevations are >5x ULN and persist beyond 2 weeks Any concerns about hepatotoxicity should be discussed promptly with the Medical Monitoring team. There are no data on the use of pretomanid in pregnancy, or during breast feeding.
Adverse Reactions*	In clinical trials of the bedaquiline-pretomanid-linezolid regimen, reported severe adverse reactions have included: • hepatotoxicity • myelosuppression, peripheral and optic neuropathy (all known adverse reactions to linezolid

	• QTc prolongation (known adverse reaction to bedaquiline) Pre-clinical animal studies reported testicular atrophy and fertility problems. Potential effects on human male fertility are still being evaluated.
Contraindications	Pretomanid should always be initiated as part of a treatment regimen including bedaquiline and linezolid, so it is contraindicated if these drugs are contra-indicated. After treatment initiation: If bedaquiline is discontinued, pretomanid must also be discontinued, and the entire regimen should be re-assessed. If linezolid is permanently discontinued during the initial four consecutive weeks of treatment, the bedaquiline-pretomanid-linezolid regimen should also be discontinued and the entire treatment regimen should be re-assessed. If linezolid is discontinued after the initial four weeks of consecutive treatment, the bedaquiline-pretomanid regimen may be continued.
Drug Interactions*	CYP3A4 Inducers: Co-administration of pretomanid with rifampicin and efavirenz may result in a decrease in pretomanid plasma concentrations. Avoid co-administration of the combination bedaquiline-pretomanid-linezolid regimen with rifampin, efavirenz, or other strong or moderate CYP3A4 inducers. Lopinavir/ritonavir (LPV/r): Co-administration of pretomanid with LPV/r did not affect the plasma concentrations of pretomanid. LPV/r can be co-administered with the combination bedaquiline-pretomanid-linezolid regimen.
Guidance on monitoring	ECG before initiation of treatment. Check serum potassium, calcium and magnesium and correct abnormalities before initiation of treatment. Assess for symptoms and signs of liver disease (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly and check LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) before initiation of treatment. Monitor clinically and biochemically for hepatotoxicity during treatment.
Linezolid	
Activity against TB, Mechanism of action, and metabolism	Bactericidal: Inhibits protein synthesis.

Dose	Adults: 600 mg, once daily. (Reduce to 300 mg/day if serious adverse effects develop). Ongoing trials may inform on revised dosing. Vitamin B6: All participants should receive vitamin B6 while receiving linezolid.
Special Circumstances	Use in renal disease: No dose adjustment is recommended, but metabolites may accumulate. Use in hepatic disease: Rarely associated with increased transaminases. Use in pregnancy/breastfeeding: Not recommended during pregnancy or breastfeeding due to limited data.
Adverse Reactions*	Common: diarrhoea, nausea, vomiting, headache, transient increases in LFTs. Serious: myelosuppression (decreased level of platelets, white blood cells, and/or anaemia), optic and peripheral neuropathy (increased risk with prolonged treatment and may be irreversible) lactic acidosis (may present recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level).
Contraindications	Hypersensitivity to oxazolidinones. Symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities).
Drug Interactions*	Avoid concurrent use with serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants etc., as it may cause serious neurological reactions such as seizures and serotonin syndrome.
Guidance on monitoring	Monitor for peripheral neuropathy and optic neuritis (visual eye tests every two months or if symptoms develop, clinical examination for peripheral neuropathy monthly or if symptoms develop). Monitor a complete blood count weekly during the initial period, then monthly.
Moxifloxacin	
Activity against TB, Mechanism of action, and metabolism	Bactericidal: inhibits DNA gyrase
Dose	Adults: 400 mg daily (oral or IV)
Special Circumstances	Use in renal disease: Excretion unchanged during renal failure; no data on effect of dialysis. Use in hepatic disease: Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease. Use during pregnancy/breastfeeding: Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to observation of arthropathy in animal models. However, there are

	case reports of fluoroquinolones being used safely during pregnancy.
Adverse Reactions*	Common: Nausea, vomiting, diarrhoea, dizziness, headache, transient increases in LFTs. Serious: QTc prolongation (more common in hypokalaemia, predisposing cardiac conditions, or if combined with other QTc prolonging drugs), arthralgia, tendon inflammation and/or rupture, hepatotoxicity, hypo/hyperglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc (>500ms). Fluoroquinolones may lower seizure threshold, so use with caution in participants with CNS disorders.
Drug Interactions*	Caution if used alongside other drugs known to prolong QTc.
Guidance on monitoring	Symptomatic monitoring. Some guidelines recommend ECG at baseline, 2 weeks and every 3 months thereafter, especially if concurrent use with other medicines which may prolong QTc.
Levofloxacin	
Activity against TB, Mechanism of action, and metabolism	Bactericidal: inhibits DNA gyrase
Dose	Adults: For treatment of TB disease 10–15 mg/kg once daily. Renal failure/dialysis: 750–1000 mg/dose, 3 times weekly (not daily) for creatinine clearance <30 ml/min.
Special Circumstances	Use in renal disease: Dosage adjustment is recommended if creatinine clearance is <50 ml/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. Use in hepatic disease: Drug concentrations are not affected by hepatic disease. Presumed to be safe in severe liver disease. Use during pregnancy/breastfeeding: Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to observation of arthropathy in animal models. However, there are case reports of fluoroquinolones being used safely during pregnancy.
Adverse Reactions*	Nausea and bloating. Headache, dizziness, insomnia or tremulousness. Rare-tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc (>500ms). Fluoroquinolones may lower seizure threshold, so use with caution in participants with CNS disorders.
Drug Interactions*	Caution if used alongside other drugs known to prolong QTc.
Guidance on monitoring	Symptomatic monitoring. Some guidelines recommend ECG at baseline, 2 weeks and every 3 months thereafter, especially if concurrent use with other medicines which may prolong QTc.

* Information on adverse reactions and drug interactions is not exhaustive. Please refer to pharmacy formulary, or discuss with the medical monitoring team as necessary.

11. DATA MANAGEMENT

All data management activities will be undertaken by the applicable regulatory frameworks and managed by CAPRISA for all sites. This includes the European Medicines Agency (EMA) regulations relating to data integrity, data protection and privacy and the relevant health products regulatory authorities of South Africa, Nigeria and Ethiopia. The TRiAD study will also abide by all relevant institutional review board regulations. The Data management systems in CAPRISA meet FDA requirements as they are Code of Federal Regulations (CFR) Part 11 compliant (the part of Title 21 of the CFR that establishes the U.S. FDA regulations on electronic records and electronic signatures). The Data Management standard processes are aligned with the Good Clinical Data Management Processes (GCDMP).

The data collection method that will be used is Electronic Data Capture (EDC) using DFexplore (5.1.0, DF/Net, Seattle, USA). DFexplore is a validated clinical database management system which is FDA CFR Part 11 compliant. Electronic Case Report Form (eCRF) data will reside on the DFexplore server housed at CAPRISA Doris Duke Medical Research Institute (DDMRI) and is backed up at regular intervals at CAPRISA DDMRI.

The electronic-CRF design will be guided by the study protocol with final approval by the study team. All study staff will be allocated user roles, specific to their function in the study. Database access will be restricted by passwords and validation levels. The study staff and statistician can access the database in “read-only” mode once data has been entered. All data roles will have write-access for data entry purposes and all data will be managed by the CAPRISA Data Management team manager. All external electronic lab data must be password protected and will be imported into DFexplore.

In the event of internet downtime, power outages, or any situation that makes the system inaccessible, one-ply paper CRFs will be used to collect the data, which will be scanned through to the CAPRISA data centre once the internet is active again. DFexplore has optical character recognition (OCR) which will read the check boxes and numerical fields on the CRFs and store them in the study database. Any fields not recognized by the OCR system will be entered manually by data encoders. Data encoders will verify all data by cross-checking the scanned version to what is captured by OCR.

All queries and/or reasons for data changes will be generated electronically and will form part of the weekly and/or monthly QC Reports that will be distributed to the appropriate study team members. Study staff also have the option of addressing any query at any time. Queries arising during validation of the data will be recorded in QC reports sent to the sites on a regular basis. Any queries from scanned CRFs resulting in a change to the database must be documented on the original CRF and rescanned. QC rates will be communicated to the site monthly. Scheduled monthly downloads will be sent to the study statistician in the SAS/CSV format. These downloads will also be made available at country level on regular interval on request.

Study staff who have access to the data on their computer systems will be trained on how to use the system and the importance of system security. Support will always be available from the data manager and IT department at CAPRISA, if any issues arise.

Breaches of data integrity, data protection and privacy are defined as any serious breach of the European General Data Protection Regulation (GDPR), EU 2016/679, for all personal data processing activities applicable under this regulation. Serious breaches of the GDPR are those related to sensitive personal data and defined as:

- Unauthorized or unlawful processing of sensitive personal data collected as part of the study is monitored by the Data Manager in accordance with the Data Management Plan. Accidental loss of sensitive personal data collected as part of the study is prevented by internal policies (included in the Data Management Plan) around access to sensitive personal data and use of electronic and paper carriers of sensitive personal data. In addition, all investigators and data collection and data management staff in TRIAD need to report loss of carriers that might contain sensitive personal data to their site-PI.
- Destruction or damage of sensitive personal data collected as part of the study is monitored by the central Data Manager and site Data Managers in accordance with the Data Management Plan.

In an event where breaches of data integrity, data protection and privacy occurs, potential breaches are reported to the Project Coordinator within 2 working days of the breach becoming known as outlined in the Policy for immediate reporting to EDCTP document.

All CRFs and source documents are to be securely stored in the participant study file in a secure double-locked, fire resistant unit with restricted access in accordance with GCP requirements. Upon completion of the study, the close-out site monitoring visit and finalization of the database for analysis, any original forms will be bound and kept for long term storage.

12. STUDY COMMITTEES

12.1. Joint Steering Committee

A consortium Joint Steering Committee (JSC) will be established in order to manage the overall collaboration and make decisions in accordance with the research collaboration agreement.

Committee accountabilities will include:

- Oversight of the TRiAD project
- Approve project plans, study protocol, and communication/publication plans
- Ensure that all necessary regulatory authority and ethics committee approvals have been obtained
- Take relevant decisions to enable the conduct of the project and the achievement of agreed deliverables

The JSC will consist of one member from each of the collaborating organizations. The lead participant of coordinating institution of the project will be the chairperson of the JSC. Other parties, including but not limited to project funders, may be invited to send one or more representatives to participate in JSC meetings. These additional parties are entitled to participate in the JSC meetings and contribute to discussions but may not vote on decisions to be taken by the JSC. In detail, a member of EDCTP will act as observer on the JSC. The JSC will meet routinely once a quarter though additional meetings may be scheduled by the chairperson, as required.

A quorum for the JSC meeting will be two thirds representation of the consortium, in addition to the chairperson. Since senior members from each collaborating organisation serve on the JSC, it is able to make decisions rapidly, if needed. The JSC will also ensure that the project activities are in accordance with the collaborative agreement and funders requirements. The JSC will have equal representation from all institutions directly involved in the project. The chairperson of the JSC may appoint an ethics advisor to participate in deliberations on any ethical matters that are on the JSC agenda. The main purpose of the JSC is to enhance sharing of information and ensure effective communication of each partner's trial-related activities. Final decision-making processes will be based on a consensus approval.

12.2. Medical Monitoring Team (MMT)

A MMT will be established for the study. The overall objective of medical monitoring is to enhance the consistency of participant management within the context of the protocol. This improves participant safety and enhances the consistency of the data emerging from the study. The MMT will work with the Principal Investigators, and Site Investigators to ensure:

1. Adequate safety oversight of study participants
2. Optimal consistency of clinical management across all sites in the TRiAD study

During the study, it will the responsibility of the MMT to respond to queries on clinical management from Site Investigators and consult with the Principal Investigator regarding any concerns which arise. When requested by an investigator, a medical monitor discusses potential participant recruitment and outcome allocations with site investigators and helps to ensure that only participants who meet the protocol inclusion and exclusion criteria are enrolled in the study. The medical monitor also offers advice on toxicity management in accordance with established study protocols are followed, and reviews data, when provided, in order to support prompt identification of potential safety concerns. The medical monitor may discuss the progress of subjects in the trial and any safety concerns that are new or are being tracked. Communication with the MMT will be by telephone and / or electronic means as appropriate to the clinical situation. AEs and other non-urgent medical concerns will be discussed by the MMT on a regular basis with the Principal Investigator. The MMT will also advise PI's/ site-clinicians on the management of interruptions to treatment and discontinuation of treatment due to toxicity and treatment failure.

12.3. Data Safety Monitoring Board (DSMB)

Safety will be monitored internally by the medical monitoring team and externally an independent DSMB for the study. The details of the operation and responsibilities of the DSMB will be defined in a DSMB Charter. The Charter will delineate the duties, responsibilities, and

procedures of the DSMB. CAPRISA will lead the development of the Charter. The DSMB will be comprised by a statistician, and at least two experts in TB or HIV clinical studies (infectious disease specialist or clinician), all independent of the study team.

The DSMB will meet via teleconference annually and will review primary and key secondary endpoint data. Each meeting will comprise an open session, which will be attended by the study team. At the end of the open session, the DSMB will have a closed session, attended only by DSMB members. More frequent or ad hoc reviews of safety reports may be conducted by the DSMB as needed. After each DSMB meeting, the Chairperson will issue a written report describing all recommendations. The DSMB could recommend that the study should proceed as designed, should proceed with design modifications, or should be discontinued.

13. HUMAN PARTICIPANT PROTECTION AND ETHICAL OBLIGATIONS

13.1. Ethical and Regulatory Review

SOUTH AFRICA; CAPRISA/WITS Health Consortium: Ethical approval for the conduct of this study in South Africa will be sought from the UKZN Biomedical Research Ethics Committee (BREC) for ethical review for CAPRISA and the and the Human Research Ethics Committee (HREC) for WITS. Regulatory approval will be sought from South African Health Products Regulatory Authority (SAPHRA) for both clinical research sites in South Africa. These institutions are registered with the South African Department of Health's National Health Research Ethics Council (**http://www.doh.gov.za/nhrec**) (NHREC REC 200408-009), and the US Office for Human Research Protections (**http://www.hhs.gov/ohrp/**) (OHRP).

NIGERIA/IHVN: Ethical approval for the conduct of this study in Nigeria will be sought from the Nigerian National Health and Research Ethics Committee of Nigeria (NHREC), the IRB of the University of Maryland, Baltimore, (UMB) (the country PI is also a Professor of Medicine at UMB), and the health research ethics committees of all the participating clinics sites.

ETHIOPIA/EPHI: Ethical approval for the conduct of this study in Ethiopia will be sought from the Scientific and Ethical Review Office (SERO) which is the office of the secretariat for the institutional review board of Ethiopian Public Health Institute (EPHI). The protocol reviewed by EPHI-IRB will be submitted to National Research Ethics Review Committee (NRERC) as it involves human participants and new diagnostic that are not registered for use in Ethiopia.

13.2. Informed consent process

Written informed consent will be obtained from each study participant prior to screening and enrolment. Written informed consent will also be obtained for long-term specimen storage and possible future analyses. Participants will be provided with a copy of their informed consent forms if they wish to receive them.

Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be

translated into respective languages for each country and the accuracy of the translation will be verified through independent back-translation.

The study consent process will include an assessment of each potential participant's understanding of the study and the risks and benefits of study participation, which are essential for an informed decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

Only participants who give informed consent per IRB/IEC requirements will be enrolled in the protocol. Potential participants will have the requirements of the protocol explained to them and they will have the opportunity to discuss the protocol with the site investigator or designee before consent is obtained. They will be assured that their decision to participate is voluntary and made completely without prejudice to their future care and treatment. Once the study team member is satisfied that the participant has understood the requirements of the protocol and the informed consent form (ICF), the participant will be asked to sign and date the ICF. The originals will be retained in the clinical research unit's research file and a copy will be provided to the participant. Participants may refuse to participate in this protocol. If they decide to participate, they may change their minds and discontinue after the study has started without facing penalties or loss of benefits. This will be monitored continuously throughout the study period. If the participant decides to leave the study, he/she can notify the PI or designee. If enrolled participants want to withdraw their consent for long-term storage and possible future research testing of their biological samples, they can simply contact the PI or designee. The samples remaining in storage will be destroyed and documented in the laboratory management system.

13.3. Participant Confidentiality

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. All participant data including laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ethics committee or the sponsor's designee. External monitors will also review clinical information. QA officers and Head of QA will not be on delegation of Authority Log as these staff serve as internal and/or external monitors.

13.4. In-country Regulations of diagnostics and study drugs

Each participating clinical research site:

- Needs to attain the relevant Institutional Review Board/Ethics Committee approvals for the study
- Is responsible for all necessary regulatory approvals for the study, and shall prepare, file and hold all applicable regulatory approvals for the study

- Is also solely responsible for all regulatory obligations associated with the study, including the collection and submission of all applicable regulatory information (including adverse events) to the appropriate in-country regulatory authority
- Is responsible for sourcing all necessary import permits and material transfer agreements

A study specific drug and diagnostic management SOP contains details relating to the supply and management of study products as well as on-site storage and accountability.

13.5. Good Clinical Practice

South Africa: The study will be carried out according to ICH-GCP and South African Good Clinical Practice Guidelines (SA GCP). The PI and/or designee will ensure that the study staff are conducting the study in accordance with current SA GCP and ICH-GCP guidelines, ensure appropriate human participants training for all study staff and safety of all study participants. The study protocol and participant informed consents and all future revisions of these latter documents will be reviewed and approved by UKZN BREC and SAPHRA prior to implementation. Quality control officers will perform daily quality checks on participant data and the Data manager will oversee the maintenance and completeness of the participant data.

All Serious Adverse Events (SAE's) will be reported to UKZN BREC and SAPHRA within 7 business days of site awareness. The DSMB will meet at designated timepoints to analyse and discuss safety data and make recommendations for the continuation of the study and participant care.

Nigeria: All study activities will be performed in accordance with the ICH-GCP guidelines and the NHREC code of conduct. Under the leadership of the Country PI, appropriate trainings on research ethics will be provided for the study team and clinic site personnel involved in the study implementation. Certificates from these trainings will be archived for reference purposes.

In line with the WHO recommendation for new medicines and regimens, active drug safety management and monitoring systems will be deployed to report SAE's and AE's of special interest. This will also be in accordance with the reporting guidelines of National Agency for Food and Drug Administration and Control (NAFDAC), as well as NHREC. To maintain high quality data capture, daily quality control checks will be performed on all filled case report forms.

Ethiopia: The study will be carried out according to ICH-GCP, Clinical Trial Authorization Guideline and National Research Ethics Review Guideline. The protocol will be approved by the national and institutional Ethics Committee. The Principal Investigator ensures the study is conducted as per the protocol. All study team will be trained on study participant enrolment, data management and security, safety of study participant.

Serious Adverse effect will be reported to the national clinical review committee and study team. The study team will ensure the recommendation is communicated and use for participant care.

14. BIOHAZARD CONTAINMENT

The research complies with applicable health and safety procedures and with applicable international and national law regarding the protection of humans, including research staff.

All precautions will be employed by all personnel during the collection of samples and all dangerous materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

Experimental assays will be conducted in a Biosafety level 3 laboratory facility. All staff and students will receive comprehensive safety training on handling of the hazardous organisms. Effective personal protective equipment will be supplied.

15. REFERENCES

1. WHO. Global tuberculosis report World Health Organization; 2018.
2. WHO. Global tuberculosis report World Health Organization; 2020.
3. Dheda K, Gumbo T, Maartens G, Dooley KE, Murray M, Furin J, et al. The Lancet Respiratory Medicine Commission: 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis. The Lancet Respiratory Medicine. 2019;7(9):820-6.
4. WHO. The End TB Strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva, Switzerland: WHO, 2015. 2016.
5. WHO. Consolidated guidelines on drug-resistant tuberculosis treatment. 2019.
6. Zhiyi Lan M, Nafees Ahmad P, Parvaneh Baghaei M, Linda Barkane M, Andrea Benedetti P, Sarah K Brode M, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. The Lancet 2020;8(3).
7. WHO. Largest ever roll-out of GeneXpert® rapid TB test machines, in 21 countries. World Health Organization. 2013.
8. WHO. Next-generation Xpert® MTB/RIF Ultra assay recommended by WHO. World Health Organization; 2017.
9. WHO. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance.: World Health Organization; 2016. Report No.: 9241510560.
10. Tomasicchio M, Theron G, Pietersen E, Streicher E, Stanley-Josephs D, Van Helden P, et al. The diagnostic accuracy of the MTBDRplus and MTBDRsl assays for drug-resistant TB detection when performed on sputum and culture isolates. Scientific reports. 2016;6:17850.
11. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2017;17(2):223-34.
12. Olayanju O, Limberis J, Esmail A, Oelofse S, Gina P, Pietersen E, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. European Respiratory Journal. 2018;51(5):1800544.
13. WHO. Treatment guidelines for drug-resistant tuberculosis: World Health Organization; 2016.
14. Nunn AJ, Phillips PP, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. New England Journal of Medicine. 2019;380(13):1201-13.
15. Zhao Y, Fox T, Manning K, Stewart A, Tiffin N, Khomo N, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: a retrospective cohort study. Clinical Infectious Diseases. 2018;68(9):1522-9.
16. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. New England Journal of Medicine. 2020;382(10):893-902.
17. WHO. Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. 2019.
18. Li S-Y, Tasneen R, Tyagi S, Soni H, Converse PJ, Mdluli K, et al. Bactericidal and sterilizing activity of a novel regimen with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. Antimicrobial agents and chemotherapy. 2017;61(9):e00913-17.
19. Dawson R, Harris K, Conradie A, Burger D, Murray S, Mendel C, et al., editors. Efficacy of bedaquiline, pretomanid, moxifloxacin & PZA (BPAMZ) against DS-& MDR-TB.

Conference on Retroviruses and Opportunistic Infections (CROI), CROI Foundation in partnership with the International Antiviral Society-USA, Seattle, WA; 2017.
20. ClinicalTrials. Trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) Adult Patients and Drug-Resistant (DR-TB) Adult Patients. National Library of Medicine (US). 2017:Identifier NCT03338621.
21. Kendall EA, Malhotra S, Cook-Scalise S, Denkinger CM, Dowdy DW. Estimating the impact of a novel drug regimen for treatment of tuberculosis: a modeling analysis of projected patient outcomes and epidemiological considerations. BMC infectious diseases. 2019;19(1):794.
22. Xie YL, Chakravorty S, Armstrong DT, Hall SL, Via LE, Song T, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. New England Journal of Medicine. 2017;377(11):1043-54.
23. Cao Y, Parmar H, Gaur RL, Lieu D, Raghunath S, Via N, et al. Xpert MTB/XDR: a 10-Color Reflex Assay Suitable for Point-of-Care Settings To Detect Isoniazid, Fluoroquinolone, and Second-Line-Injectable-Drug Resistance Directly from Mycobacterium tuberculosis-Positive Sputum. Journal of Clinical Microbiology. 2021;59(3).
24. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. The Lancet Infectious Diseases. 2018;18(1):76-84.
25. Gillespie SH, Sabiiti W, Oravcova K. Mycobacterial load assay. Diagnostic Bacteriology: Springer; 2017. p. 89-105.
26. Hai HT, Vinh DN, Thu DD, Hanh NT, Phu NH, Srinivasan V, et al. Comparison of the Mycobacterium tuberculosis molecular bacterial load assay, microscopy and GeneXpert versus liquid culture for viable bacterial load quantification before and after starting pulmonary tuberculosis treatment. Tuberculosis. 2019;119:101864.
27. Honeyborne I, McHugh TD, Phillips PP, Bannoo S, Bateson A, Carroll N, et al. Molecular bacterial load assay, a culture-free biomarker for rapid and accurate quantification of sputum Mycobacterium tuberculosis bacillary load during treatment. Journal of clinical microbiology. 2011;49(11):3905-11.
28. Honeyborne I, Mtafya B, Phillips PP, Hoelscher M, Ntinginya EN, Kohlenberg A, et al. The molecular bacterial load assay replaces solid culture for measuring early bactericidal response to antituberculosis treatment. Journal of clinical microbiology. 2014;52(8):3064-7.
29. Sabiiti W, Azam K, Farmer ECW, Kuchaka D, Mtafya B, Bowness R, et al. Tuberculosis bacillary load, an early marker of disease severity: the utility of tuberculosis Molecular Bacterial Load Assay. Thorax. 2020;75(7):606-8.
30. Mtafya B, Sabiiti W, Sabi I, Msuya Y, Ntinginya N. Clinical evaluation of the novel molecular bacterial load assay for real-time monitoring of tuberculosis treatment response. Access Microbiology. 2019;1(1A):284.
31. Mbelele PM, Mpolya EA, Sauli E, Mtafya B, Ntinginya NE, Addo KK, et al. Mycobactericidal effect of different regimens measured by molecular bacterial load assay among people treated for multidrug-resistant tuberculosis in Tanzania. Journal of clinical microbiology. 2021.
32. WHO. Updated definitions of extensively drug-resistant tuberculosis. 2021 27 January 2021.
33. Conradie F. NiX-TB trial experience: safety reporting and recommendations for programmatic implementation of the regimen. The 50th Union World Conference on Lung Health. 2019;Hyderabad India.
34. Evans D, Schnippel K, Govathson C, Sineke T, Black A, Long L, et al. Treatment initiation among persons diagnosed with drug resistant tuberculosis in Johannesburg, South Africa. PloS one. 2017;12(7):e0181238.
35. Cox HS, Daniels JF, Muller O, Nicol MP, Cox V, van Cutsem G, et al., editors. Impact of decentralized care and the Xpert MTB/RIF test on rifampicin-resistant tuberculosis

treatment initiation in Khayelitsha, South Africa. Open forum infectious diseases; 2015: Oxford University Press.
36. Naidoo P, Du Toit E, Dunbar R, Lombard C, Caldwell J, Detjen A, et al. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. PLoS One. 2014;9(7):e103328.
37. Cox H, Dickson-Hall L, Ndjeka N, van't Hoog A, Grant A, Cobelens F, et al. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: a retrospective cohort study. PLoS medicine. 2017;14(2):e1002238.
38. Jo E-J, Park S, Lee KM, Kim I, Eom JS, Kim M-H, et al. Time to appropriate treatment in patients with multidrug-resistant tuberculosis in South Korea: Are we still in 2010? PloS one. 2019;14(4):e0216084.
39. Definitions W. Definitions and reporting framework for tuberculosis. Geneva: World Health Organization. 2020.
40. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.

16. APPENDICES

Appendix I: General guide to safety monitoring in DR-TB therapy

This information, based on WHO guidance, represents a general guide for clinicians managing participants during the TRiAD study. Information contained herein is intended to supplement Section 10.4 of the TRiAD study protocol. Specific practice at each site may vary, in accordance with National Tuberculosis Programme protocols in participating countries. The Medical Monitoring Team should be consulted as necessary to address concerns when they arise.

1. Baseline safety tests during regimen selection / before initiation of therapy

The TRiAD study protocol requires baseline data collection encompassing: medical history (including HIV status and CD4 count), clinical examination (including random blood glucose, ophthalmological examination of visual acuity and colour vision assessment, pregnancy test and peripheral neuropathy assessment), chest X-ray and laboratory safety assessments (according to in country standard of care).

The table, below, provides additional information and recommendations

Assessment / measurement	Rationale and possible actions*
Treatment management with routine Laboratory measurement abnormalities	
Baseline renal function (esp. serum potassium and creatinine)	Preferably avoid second line TB drugs (e.g. aminoglycosides or capreomycin) if there is baseline renal dysfunction
Baseline full blood count	Caution and close monitoring of linezolid use if anaemia, leukopaenia or thrombocytopenia at baseline
Baseline liver function (esp. bilirubin, ALT)	Caution with rifampicin, isoniazid, pyrazinamide, bedaquiline and pretomanid
Thyroid function test (e.g. TSH)	Caution with use of ethionamide / prothionamide and PAS
Additional considerations	
Problem of visual acuity / colour vision	Consider omitting ethambutol from treatment regimen if abnormal; caution with use of linezolid
Neurological abnormality (esp. peripheral neuropathy)	Caution with use of isoniazid, linezolid, cycloserine or terizidone Co-prescribe Vitamin B6 as preventive therapy
Psychological illness	Preferably avoid cycloserine or terizidone
ECG	Caution with use of QTc prolonging drugs (esp. bedaquiline, fluoroquinolones, clofazimine, delamanid) if baseline QTc >450ms Preferably avoid these drugs if QTc <500ms
Audiometry	Perform wherever possible if planning to initiation injectable second line TB drugs (aminoglycosides or capreomycin); however, preferably avoid these drugs, esp. if there is any baseline abnormality

***Discuss points of concern with Medical Monitoring Team.**

2. Safety monitoring during DR-TB treatment

Monitoring evaluation	Recommended frequency*
Routine Laboratory measurements as per in-country guideline	
Renal function (esp. serum potassium and creatinine)	At baseline, then monthly if possible while receiving an injectable agent Consider more frequently in higher risk groups (e.g. HIV-infected participants, diabetics, known underlying renal disease)
Serum magnesium and calcium	Check, if possible, when hypokalaemia is diagnosed Repeat check potassium, magnesium, calcium if QTc prolongation or cardiac arrhythmias
Liver function (bilirubin, ALT)	Check monthly on rifampicin, isoniazid, pyrazinamide, bedaquiline and pretomanid containing regimens Frequency may be gradually reduced if stable, or may be more frequent in high-risk groups (e.g. underlying liver disease, viral hepatitis)
Full blood count	If on linezolid, check weekly at first then monthly (may reduce frequency in longer-term use if stable)
TSH	Check every 3 months if receiving both ethionamide/prothionamide and PAS Check every six months if receiving one of ethionamide/prothionamide *or* PAS Also monitor for clinical signs of hypothyroidism if using those drugs
Lactic acid	Check if concern of lactic acidosis on linezolid and / or antiretroviral therapy
Additional considerations	
Visual, neurological and psychological evaluations	Perform according to clinical concern at each consultation
ECG	Repeat during treatment; frequency dependent on specific QTc prolonging drugs in treatment regimen, and other cardiac risk factors
Audiometry	Repeat monthly, if possible, whilst on second-line injectable drugs

***Discuss emergent abnormalities with Medical Monitoring Team (consider: is there a need for symptomatic therapy, dose change, treatment interruption, or change of regimen?).**

3. Initial management of common adverse events

Adverse events should be reported according to Sections 10.1 – 10.3 of the protocol. The table below provides additional information but is not exhaustive. Support should be sought from the Medical Monitoring Team as necessary.

Adverse event	Likely drug	Initial management	Comment
Rash / allergy / anaphylaxis	Any drug	If serious reaction, stop therapy and manage according to emergency protocols Eliminate other potential allergens Minor dermatological reactions may be treated with antihistamines and topical/systemic corticosteroids	Dry skin and chronic skin discolouration are common, sometimes problematic, side-effects of with clofazimine Re-introduction of drugs should be discussed with the PI and Medical Monitoring Team; any drug causing anaphylaxis or Stevens-Johnson-Syndrome should never be reintroduced All allergies should be noted on the CRF and in the participant's medical record
Nausea / vomiting / diarrhoea / abdominal pain	Any drug, esp. Ethionamide / Prothionamide, PAS	Symptomatic therapy including hydration and anti-emetics Investigate potential causes including the risk of underlying systemic toxicity (e.g. lactic acidosis, liver dysfunction) Check electrolytes, especially if using QTc prolonging medications Consider adjusting timings / doses of suspected drugs	Temporarily suspending suspect drugs may be necessary Some anti-emetic drugs (e.g. ondansetron) can also prolong the QTc; be cautious monitor closely if concurrently using QTc prolonging anti-TB medications Antacids may interfere with absorption of fluoroquinolones; avoid concurrent use

Adverse event	Likely drug	Initial management	Comment
Hepatotoxicity	Rifampicin, isoniazid, pyrazinamide, bedaquiline, pretomanid	Stop treatment if • Any ALT elevation is accompanied by a bilirubin elevation >2x ULN • ALT is >8 x ULN • ALT is >5x ULN and persist beyond 2 weeks	Eliminate other potential causes of liver toxicity (e.g. viral hepatitis, alcohol, concurrent medications) Re-introduction of drugs, after interruption, should be discussed with the PI and Medical Monitoring Team

		Continue to monitor liver function until it returns to normal; seek specialist support for progressive disease	
Hypothyroidism	Ethionamide / prothionamide, PAS	Can be treated with levothyroxine and TSH monitoring	Usually completely reversible on completion of therapy.
Arthralgia	Pyrazinamide / fluoroquinolones, bedaquiline	Check urate, treat with non-steroidal anti-inflammatory drugs if possible Consider dose reduction or interruption of suspect drug, if symptoms are severe	Rarely, severe tendonitis and tendon rupture can occur with fluoroquinolones; should significant tendon inflammation be suspected consider stopping the fluoroquinolone
Nephrotoxicity	Injectable second line drugs	Monitor renal function and serum electrolytes closely Consider reducing to thrice weekly dosing or changing to an all-oral treatment regimen if possible	First-line recommendations for DR-TB now avoid nephrotoxic injectable drugs whenever possible
Deafness / vestibular toxicity (dizziness and tinnitus	Injectable second line drugs	Consider reducing to thrice weekly dosing or changing to an all-oral treatment regimen if possible	Hearing loss from injectable drugs can be permanent: first-line recommendations for DR-TB now avoid nephrotoxic injectable drugs whenever possible

Adverse event	**Likely drug**	**Initial management**	**Comment**
Peripheral neuropathy	Cycloserine / terizidone, linezolid, isoniazid	Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200mg /day) Simple and neuropathic analgesia Consider whether drug doses can be reduced without compromising the regimen. Switching potential culprit drugs to alternatives may be necessary	Be mindful of other potential contributors to multi-factorial neuropathy (e.g. HIV, ART, diabetes, hypothyroidism, alcohol)
Psychological upset (depression / psychosis)	Cycloserine / terizidone	Dose reduction or stopping the drug may be necessary.	Consider all potential contributors to psychological problems

			– seek specialist support as appropriate
Visual disturbance / optic neuritis	Ethambutol / linezolid	Stop suspect drug Seek ophthalmology support	Ethambutol is typically associated with colour blindness
Lactic acidosis	Linezolid	Stop linezolid	Consider other potential causes of lactic acidosis (e.g. ART, sepsis)
QTc prolongation	Bedaquiline, delamanid, fluoroquinolones, clofazimine	Check that potassium, calcium and magnesium levels are in the normal range Avoid other drugs which increase the QTc Consider suspension / discontinuation of QTc prolonging drugs if the cardiac risk outweighs the potential benefit	Intensified ECG monitoring is indicated if QTc >450ms Consideration of suspending possible culprit drugs if QTc >500ms Greater caution required in participants with underlying cardiac disease
Haematological abnormalities	Linezolid	Consider dose reduction or suspension of linezolid if progressive anaemia myelosuppression	Remember that blood dyscrasias can occasionally occur with other anti-TB drugs

Appendix II: Example of TRiAD Screening Informed Consent Form

TRiAD INFORMED CONSENT FORM: SCREENING (ENGLISH)

TITLE: A Phase 4 Operational Study to Assess the Effectiveness, Feasibility, Acceptability, and Cost-Effectiveness of Implementing the GeneXpert MTB/XDR (Xpert XDR; Cepheid) Assay for Rapid Triage-and-Treatment of DR-TB

INFORMATION FOR PARTICIPANTS

SHORT TITLE:	Triage Test for All Oral DR-TB Regimen (TRiAD Study)
PRINCIPAL INVESTIGATOR:	Prof Kogieleum Naidoo
ADDRESS:	719 Umbilo Road Doris Duke Medical Research Institute (2nd floor) Nelson R Mandela School of Medicine University of Kwa-Zulu Natal Durban, 4013
TELEPHONE:	+27 31 260 4687
ETHICS COMMITTEE:	University of KwaZulu Natal Biomedical Research Ethics Committee (UKZN BREC)

Information Sheet and Consent to Participate in Research

Instructions:

1. Please read and understand the information below
2. If you have any questions or need any explanations, please feel to discuss with the person handing you the Informed Consent Form at any time.
3. Once you have agreed to participate in the study and you will be asked to sign below. We will give a copy (if you wish to have one) and a copy will be placed in your file. The original will be kept in a secure room by the study co-ordinator

Date: _____

Dear patient,

We are performing a research study across 9 study sites in South Africa (2), Nigeria (2) and Ethiopia (5). The Principal Investigator for this site is Prof Kogieleum Naidoo, telephone number is +27 31 260 4687 and email is **kogie.naidoo@caprisa.org**.

1. Why am I being asked to volunteer?

This is a screening consent form. You are being asked to volunteer for screening tests to find out if you are eligible for a research study called the TRiAD study. We approached you to participate in this study as you have symptoms suggestive of tuberculosis (TB) in the lung or have been recently diagnosed with lung TB based on your sputum test. We wish to collect an additional sputum sample to undertake further testing for TB drug resistance on your sputum. Before you decide to participate, it is important that you understand why the research is being done and what it will involve. Please take time to consider the following information explained below before deciding whether you wish to participate in this study. We will explain this carefully but please feel free to ask questions or discuss with others.

Joining this study is voluntary and will not affect the care you receive at this site or elsewhere.

2. What is the purpose the study?

TB, caused by the bacterium Mycobacterium tuberculosis (M.tb), remains a serious infectious disease throughout the world. Some people have a form of TB that does not respond to standard drug therapy, this is called drug-resistant tuberculosis (DR-TB). Early diagnosis of drug-resistant TB will enable your health care worker to give you the most effective TB treatment.

Researchers have been searching for better ways to diagnose and treat drug resistant TB infection. Sputum samples taken from people with TB symptoms undergo routine GeneXpert testing in the laboratory. This test finds TB and also finds resistance to the TB drug rifampicin (RIF). In this study we propose using an updated version of the routine GeneXpert MTB/RIF or Ultra test called the Xpert XDR test. The Xpert XDR test will screen your sputum for presence of resistance to additional TB drugs. This test will be done before your treatment regimen is selected. Should the Xpert XDR test confirm TB and show presence of resistance to additional TB drugs, you will be contacted to enrol into our study.

3. Is it necessary for me to take part in the study?

It is important that you know the following:

- You are only being asked to provide an additional sputum for Xpert XDR testing at this time. Even if you agree to have the screening test, you do not have to join this study
- Your participation is voluntary; you do not have to have the screening Xpert XDR test if you do not want to participate in this study
- Your decision to not participate in this study will not result in losing your regular medical care
- You will receive the results of the screening test is positive and you are being considered for participation in this study

4. What do I have to do if I decide to take part in the screening tests?

If you agree to have screening sputum test, this will be done in addition to the routine TB test performed on your sputum.

Screening Visit:
The procedures done at this visit today will take 15 – 30 minutes

- You will be asked to provide the following information, in order for us to contact you, should you have a positive Xpert XDR test:
  - Contact telephone number
  - Any alternate telephone numbers
  - Where you live

- Study staff will take a sputum sample, to test your drug resistance to different TB drugs (if any)
  - You will be told your TB test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent the spread of TB. Only those with a recent valid TB test result will be considered for inclusion in this study.
  - Participants suffering clinically significant medical conditions or have previous exposure to TB drugs; Bedaquiline and/or linezolid, cannot join this study. We will tell you where you can get care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

If the sputum GeneXpert MTB/RIF or Ultra test results show that you can join the TRiAD study, you may be contacted for enrollment into the study. Participants will be enrolled in this study for 12 -18 months; however this period could be shorter or longer than anticipated. If you decide to be in this study, you will be asked to sign another consent form.

5. What are the risks and disadvantages of taking part?

There are no disadvantages of taking part in this study

6. What are the possible benefits of taking part?

The primary benefit of screening for this study is having access to the new Xpert XDR diagnostic.

7. Reasons why you may be withdrawn from the screening tests without your consent

- Sputum sample submitted is inadequate for the Xpert XDR test
- You are found not to be eligible for this study
- Other reasons identified by study staff

8. Will I receive payment?

There is no re-imbursement for the screening test.

9. Will my taking part in the study be kept confidential?

Yes. All information collected about you during the course of the research will be kept strictly confidential.

10. What happens if I am injured or have concerns?

It is unlikely that you will be injured as a result of screening for this study. If you are injured as a result of screening for this study, you will be given immediate necessary treatment for your injuries at the study site, or referred to the nearest health facility for treatment. There will be no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form. If you have any concerns about any aspect of this study, you should ask to speak to the study staff who will be able to better answer your questions.

11. What will happen to any samples I give?

All sputum samples collected will be used to determine your TB diagnosis and for detection of TB drug resistance using the routine GeneXpert MTB/RIF or Ultra, and the XPERT XDR test.

12. Contacts and Questions

If you ever have any questions about the screening tests, or if you have a research-related injury, you should contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

You will be given a copy of the information sheet and a signed consent form to keep if you wish to do so. Thank you for taking the time to read this information sheet.

SIGNATURE FOR SCREENING STUDY INFORMED CONSENT

If you have read this screening consent form (or had it explained to you), all your questions have answered, and you agree to provide a sputum sample for Xpert XDR testing and take part in this study, please sign your name below:

_____	_____	_____
Participants Name (Print)	Participants Signature	Date
_____	_____	_____
Study Staff Conducting the Consent (Print)	Study Staff Signature	Date
_____	_____	_____
Witness's Name (Print) (If Applicable)	Witness's Signature	Date

Appendix III: Example of TRiAD Enrolment Informed Consent Form – Cohort 1

TRiAD INFORMED CONSENT FORM: STUDY ENROLMENT IN COHORT 1 (ENGLISH)

TITLE: A Phase 4 Operational Study to Assess the Effectiveness, Feasibility, Acceptability, and Cost-Effectiveness of Implementing the GeneXpert MTB/XDR (Xpert XDR; Cepheid) Assay for Rapid Triage-and-Treatment of DR-TB

INFORMATION FOR PARTICIPANTS

SHORT TITLE:	Triage Test for All Oral DR-TB Regimen (TRiAD)
PRINCIPAL INVESTIGATOR:	Prof Kogieleum Naidoo
ADDRESS:	719 Umbilo Road Doris Duke Medical Research Institute (2nd floor) Nelson R Mandela School of Medicine University of Kwa-Zulu Natal Durban, 4013
TELEPHONE:	+27 31 260 4687
ETHICS COMMITTEE:	University of KwaZulu Natal Biomedical Research Ethics Committee (UKZN BREC)

Information Sheet and Consent to Participate in Research

Instructions:

1. Please read and understand the information given below
2. If you have any questions or need any explanations, then please feel to discuss with the person handing you the Informed Consent Form at any time.
3. Once you have agreed to participate in the study and you will be asked to sign the enrollment informed consent form. We will give a copy (if you wish to have one) and a copy will be placed in your file. The original will be kept in a secure room by the study coordinator

Date: _____

You are being invited to take part in this research study because you have recently been diagnosed with drug resistant TB based on your **sputum test results** and are therefore eligible for **a short oral drug resistant tuberculosis treatment regimen**. The doctor in charge of this study is Dr Kogieleum Naidoo. Before you decide if you want to enroll in this study, we want you to know more about the study.

This consent form gives you information about this study, which will be done at King DinuZulu Hospital Complex in Durban. Please ask questions and discuss any concerns you may have with the research staff. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this consent form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you will still receive the same medical care as determined by your doctor.
- You may stop taking part in the study at any time and this will not affect the care you receive at the hospital.
- You may contact the Biomedical Research Ethics Committee (BREC) on 031-260 4769 or 031-260 1074 (business hours) if you have questions about your rights as a research subject.

1. What is the purpose the study?

The purpose of this study is to help doctors to rapidly identify and treat drug-resistant TB with the best available drugs. By allowing us to ask questions, collect information, and collect monthly sputum samples from you we will be able to assess the relationship between better diagnosis and treatment of drug resistant tuberculosis on treatment outcomes for drug-resistant tuberculosis.

2. How many people will take part in this study?

Approximately 320 participants will take part in this study.

3. What is involved in this study?

If you would like to participate in this study, you will be asked questions about your medical history and any medicines that you have taken. If you agree to participate in the study, we will collect medical information including results of blood tests, X- rays and sputum tests from your medical records. During your enrollment and follow-up visits, we will ask you to produce sputum samples which will be collected, processed and stored for future analysis

You will be requested to visit the clinic for study visits in two weeks, and monthly thereafter for about 6 months (while you receive the entire short-course TB treatment regimen, or during the intensive phase of TB treatment if you are receiving a longer regimen). Thereafter, we will see you at the clinic three-monthly until 12 months since your TB diagnosis. We will still maintain telephonic contact with you every three months until about 18 months since TB diagnosis, irrespective of whether or not you are still receiving TB treatment.

Use of Data/Specimens
For this study we will share your sputum, samples with other researchers at another institution (collaborators at San Raffaele Scientific Institute in Italy) so that other research studies can be done. If your sputum sample is shared with the other institution, your identifying information will not be included. If you agree to let us keep your samples for future research, your sputum will be stored at the CAPRISA Research Laboratory for 10 years. If we are required to perform any additional tests on your sputum, CAPRISA will contact the Biomedical Research Ethics Committee for approval. There will be no additional medications given to you, other than the standard medications your doctors prescribe for you.

4. How long will I be in the study?

You will be followed-up actively through the course of your drug-resistant tuberculosis treatment and through telephonic calls afterwards to a maximum of 18 months.

5. Are there benefits to taking part in this study?

If you participate in this study, you will likely receive a faster and more comprehensive diagnosis of drugs that you are resistant. You will possibly be cured sooner with a shorter duration of only 6-12 months treatment. However, should you have severe disease as determined by your doctor, the regimen selected maybe longer i.e. up to 18 months

6. What are the potential risks associated with this study?

There is a possibility of failure of the short regimens to provide intended therapeutic effect. In such cases you will be given treatment as per the sputum drug susceptibility results. There is a potential risk for psychological distress from attending study related visits. Please note that you can withdraw from the study at any time.

7. What about confidentiality and sharing information?

We are collecting information on enrolled patients as the tests and drugs used in this study are new to the TB program. The information we get from this study may help us to treat future patients with drug-resistant TB better. The results of clinical tests performed as part of this study will in your confidential medical record. The information that we collect from you will be kept confidential, using an anonymous identifier. Clinical staff, sponsor and/or its representatives, and regulatory agencies may access your clinical records. The information and results from this study, if published in scientific journals or presented at scientific meetings, will be unlinked to your name (made anonymous).

8. What other choices do I have besides this study?

If you choose not to participate in this study, you can still receive medical treatment at King DinuZulu referral hospital.

9. Will I receive payment?

You will be compensated R300 for each study visit for your time and effort provided in participating in the research. For the follow-up visits you will also be compensated R300.

10. What are the costs to me?

Taking part in this study will not involve additional costs to you. Treatment for drug resistant TB and HIV is provided at no cost according to the practices and policies of King DinuZulu referral hospital and the KwaZulu-Natal Department of Health.

11. What happens if I am injured or have concerns?

It is unlikely that you will be injured as a result of enrollment for this study. If you are injured as a result of enrolling for this study, you will be given immediate necessary treatment for your injuries at the study site, or referred to the nearest health facility for treatment. There will be no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form. If you have any concerns about any aspect of this study, you should ask to speak to the study staff who will be able to better answer your questions.

12. What if I decide not to participate in the study?

Taking part in this study is your choice. You may choose to either take part or not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

13. Contacts and Questions

- If you have any questions while taking part in this research study, you should contact the Principal Investigator: Dr. Kogie Naidoo
  Telephone: +27 31 566 0500
  Email: **Kogie.naidoo@caprisa.org**

- For questions about your rights as a research participant, or any problems related to the study you may contact: Biomedical Research Ethics Committee (BREC)
  Research Office, Westville Campus
  Govan Mbeki Building
  Private Bag X 54001
  Durban 4000
  KwaZulu-Natal, SOUTH AFRICA
  Tel: 27 31 2604769 (business hours) - Fax: 27 31 2604609
  Email: **BREC@ukzn.ac.za**

- If you have any questions regarding the study that was not answered to your satisfaction by your doctor and the Ethics Committee, you should write to The South African Health Products Regulatory Authority (SAHPRA) at:
  The Registrar
  SAHPRA
  Department of Health
  Private Bag X828
  PRETORIA
  0001

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

If you agree to participate you will be given a copy of the information sheet and a signed consent form to keep if you wish to do so. Thank you for taking the time to read this information sheet.

INFORMED CONSENT SIGNATURE FOR STUDY ENROLMENT

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate.

1. **I give my permission to participate in the study**

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

2. **I give my permission for my samples to be collected and stored for future research use**

Samples will be collected and stored for future research use. For this study we may share your sputum samples with other researchers at other institutions so that other research studies can be done now or in the future. If your sputum samples are shared with other institutions, your identifying information will not be included. The research team may use these samples to confirm test results or to do additional new tests if required. Your samples will not be sold or used in other products that make money for researchers. To protect your identity your sample container will not have your name or any information that may identify you. Only your participant number will be used on sample containers.

Any studies that use your samples will be reviewed by the Biomedical Research Ethics Committee of the University of KwaZulu Natal.

The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed. This is because research tests are often done with experimental procedures so the results from one study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify the study doctor who will try to contact you or your regular doctor. If you wish to be notified of this type of test result, you need to make sure that you contact the study nurse or doctor with any changes to your phone number or address. If you want your regular doctor to be told about this kind of test result, you need to provide the study team with the contact details of your regular doctor.

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

3. **I give my permission for any collected samples to be shipped to collaborators outside of South Africa.**

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

4. **I give my permission for Telephonic Contact**

If you cannot come to the CAPRISA offices at KDH for your study visit, study staff will contact you on your cell phone or home phone to complete study questionnaires. Study staff will ask you to go to a quiet place where you cannot be disturbed so you may answer confidential questions.

☐ YES, I agree to be contacted telephonically by CAPRISA staff to complete study questionnaires

☐ NO, I do not agree to be contacted telephonically by CAPRISA staff to complete study questionnaires

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

Appendix IV: Example of TRiAD Enrolment Informed Consent Form – Cohort 2

TRiAD INFORMED CONSENT FORM: STUDY ENROLMENT IN COHORT 2 (ENGLISH)

TITLE: A Phase 4 Operational Study to Assess the Effectiveness, Feasibility, Acceptability, and Cost-Effectiveness of Implementing the GeneXpert MTB/XDR (Xpert XDR; Cepheid) Assay for Rapid Triage-and-Treatment of DR-TB

INFORMATION FOR PARTICIPANTS

SHORT TITLE:	Triage Test for All Oral DR-TB Regimen (TRiAD)
PRINCIPAL INVESTIGATOR:	Prof Kogieleum Naidoo
ADDRESS:	719 Umbilo Road Doris Duke Medical Research Institute (2nd floor) Nelson R Mandela School of Medicine University of Kwa-Zulu Natal Durban, 4013
TELEPHONE:	+27 31 260 4687
ETHICS COMMITTEE:	University of KwaZulu Natal Biomedical Research Ethics Committee (UKZN BREC)

Information Sheet and Consent to Participate in Research

Instructions:

1. Please read and understand the information given below
2. If you have any questions or need any explanations, then please feel to discuss with the person handing you the Informed Consent Form at any time.
3. Once you have agreed to participate in the study and you will be asked to sign the enrollment informed consent form. We will give a copy (if you wish to have one) and a copy will be placed in your file. The original will be kept in a secure room by the study coordinator

Date: _____

You are being invited to take part in this research study because you have been diagnosed with resistance to one TB drug based on your recent **sputum test results.** You are therefore eligible for **an alternate standard TB treatment regimen.** The doctor in charge of this study is Dr Kogieleum Naidoo. Before you decide if you want to enroll in this study, we want you to know more about the study.

This consent form gives you information about this study, which will be done at King DinuZulu Hospital Complex in Durban. Please ask questions and discuss any concerns you may have with the research staff. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this consent form to keep.

Please note that:

- Your participation in this study is entirely voluntary. You may decide not to participate in the study, but you will still receive the same medical care as determined by your doctor.
- You may stop taking part in the study at any time and this will not affect the care you receive at the hospital.
- You may contact the Biomedical Research Ethics Committee (BREC) on **031-260 4769 or 031-260 1074** (business hours) if you have questions about your rights as a research subject.

1. What is the purpose the study?

The purpose of this study is to help doctors to rapidly identify and treat drug-resistant TB with the best available drugs. By allowing us to ask questions, collect information from the DR TB program on your progress with treatment and results of sputum samples we will be able to assess the relationship between better diagnosis and treatment of drug resistant tuberculosis, on drug-resistant tuberculosis treatment outcomes.

2. How many people will take part in this study?

Approximately 100 participants will take part in this study.

3. What is involved in this study?

If you would like to participate in this study, you will be asked questions about your medical history and any medicines that you have taken. If you agree to participate in the study, we will see you at our clinic for an enrollment visit only where we will collect medical information including results of blood tests, X- rays and sputum tests from interviewing you and from your medical records. At this visit a sputum sample will be collected from you. This sample will be processed and stored for future analysis. Although we do not require you to attend any further research visits, we will collect all clinical and laboratory information for this episode of TB from your clinical records.

We will maintain telephonic contact, monthly for six months and 3-monthly thereafter, until 6 months after the end of your TB treatment.

Use of Data/Specimens
For this study we will share your sputum samples with other researchers at another institution (collaborators at San Raffaele Scientific Institute in Italy) so that other research studies can be done. If your sputum sample is shared with the other institution, your identifying information will not be included. If you agree to let us keep your samples for future research, your sputum will be stored at the CAPRISA Research Laboratory for 10 years. If we are required to perform any additional tests on your sputum, CAPRISA will contact the Biomedical Research Ethics Committee for approval. There will be no additional medications given to you, other than the standard medications your doctors prescribe for you.

4. How long will I be in the study?

You will be followed up telephonically after this visit for 6 months after TB treatment .

5. Are there benefits to taking part in this study?

If you participate in this study, there may be a direct benefit to you. you will likely receive a more comprehensive diagnosis of drugs that you are resistant to faster. We believe that the diagnostic and drugs used in this study may significantly improve your TB treatment outcomes, but no guarantee can be made. It is important to note that there are no significant risks or benefits for you to produce a sputum sample.

6. What are the potential risks associated with this study?

There is a possibility of failure of the short/new regimens to provide intended therapeutic effect. In such cases you will be given treatment as per the sputum drug susceptibility results. There is a potential risk for psychological distress from attending study related visits. Please note that you can withdraw from the study at any time.

7. What about confidentiality and sharing information?

We are collecting information on enrolled patients as the tests and drugs used in this study are new to the TB program. The information we get from this study may help us to treat future patients with drug-resistant TB better. The results of clinical tests performed as part of this study will in your confidential medical record. The information that we collect from you will be kept confidential, using an anonymous identifier. Clinical staff, sponsor and/or its representatives, and regulatory agencies may access your clinical records. The information and results from this study, if published in scientific journals or presented at scientific meetings, will be unlinked to your name (made anonymous).

8. What other choices do I have besides this study?

If you choose not to participate in this study, you can still receive medical treatment at King DinuZulu referral hospital.

9. Will I receive payment?

You will be compensated R300 for the enrolment visit only

10. What are the costs to me?

Taking part in this study will not involve additional costs to you. Treatment for drug resistant TB and HIV is provided at no cost according to the practices and policies of King DinuZulu referral hospital and the KwaZulu-Natal Department of Health.

11. What happens if I am injured or have concerns?

It is unlikely that you will be injured as a result of enrollment for this study. If you are injured as a result of enrolling for this study, you will be given immediate necessary treatment for your injuries at the study site, or referred to the nearest health facility for treatment. There will be no compensation provided for research related injuries. You do not give up any legal rights by signing this consent form. If you have any concerns about any aspect of this study, you should ask to speak to the study staff who will be able to better answer your questions.

12. What if I decide not to participate in the study?

Taking part in this study is your choice. You may choose to either take part or not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

13. Contacts and Questions

- If you have any questions while taking part in this research study, you should contact the Principal Investigator: Dr. Kogie Naidoo
  Telephone: +27 31 566 0500
  Email: **Kogie.naidoo@caprisa.org**

- For questions about your rights as a research participant, or any problems related to the study you may contact: Biomedical Research Ethics Committee (BREC)
  Research Office, Westville Campus
  Govan Mbeki Building
  Private Bag X 54001
  Durban 4000
  KwaZulu-Natal, SOUTH AFRICA
  Tel: 27 31 2604769 (business hours) - Fax: 27 31 2604609
  Email: **BREC@ukzn.ac.za**

- If you have any questions regarding the study that was not answered to your satisfaction by your doctor and the Ethics Committee, you should write to The South African Health Products Regulatory Authority (SAHPRA) at:
  The Registrar

SAHPRA
Department of Health
Private Bag X828
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Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

If you agree to participate you will be given a copy of the information sheet and a signed consent form to keep if you wish to do so. Thank you for taking the time to read this information sheet.

INFORMED CONSENT SIGNATURE FOR STUDY ENROLMENT

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate.

1. I give my permission to participate in the study

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

2. I give my permission for my samples to be collected and stored for future research use

Samples will be collected and stored for future research use. For this study we may share your sputum samples with other researchers at other institutions so that other research studies can be done now or in the future. If your sputum samples are shared with other institutions, your identifying information will not be included. The research team may use these samples to confirm test results or to do additional new tests if required. Your samples will not be sold or used in other products that make money for researchers. To protect your identity your sample container will not have your name or any information that may identify you. Only your participant number will be used on sample containers.

Any studies that use your samples will be reviewed by the Biomedical Research Ethics Committee of the University of KwaZulu Natal.

The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed. This is because research tests are often done with experimental procedures so the results from one study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify the study doctor who will try to contact you or your regular doctor. If you wish to be notified of this type of test result, you need to make sure that you contact the study nurse or doctor with any changes to your phone number or address. If you want your regular doctor to be told about this kind of test result, you need to provide the study team with the contact details of your regular doctor.

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

3. **I give my permission for any collected samples to be shipped to collaborators outside of South Africa.**

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)

4. **I give my permission for Telephonic Contact**

Study staff will contact you on your cell phone or home phone to complete study questionnaires. Study staff will ask you to go to a quiet place where you cannot be disturbed so you may answer confidential questions.

☐ YES, I agree to be contacted telephonically by CAPRISA staff to complete study questionnaires

☐ NO, I do not agree to be contacted telephonically by CAPRISA staff to complete study questionnaires

_____	_____	_____
Participants Name (Print)	Participants Signature	Date (dd/mm/yr)