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TB-CHAMP: Tuberculosis Child Multidrug- resistant Preventive Therapy Trial

A phase III cluster-randomised placebo-controlled trial to assess
the efficacy of preventive therapy in child and adolescent
contacts of multidrug- resistant (MDR) tuberculosis (TB)

Version: 3.0

Date: 09 February 2021

ISRCTN #: ISRCTN92634082

Authorised by:

Name: Anneke C. Hesselting
Role: Principal
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Date: 9 February 2021

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GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. The MRC CTU endorses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative. It describes the TB-CHAMP trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), hereafter referred to MRC CTU, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Infections Theme, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), as laid down by the ICH topic E6 (Note for Guidance on GCP) and applicable South African and British national regulations.

SPONSOR

Stellenbosch University, South Africa is the trial sponsor and has delegated responsibility for the overall management of the TB-CHAMP trial to the MRC CTU. Queries relating to sponsorship of this trial should be addressed to the Principal Investigator (PI) at Stellenbosch University or via the trial team.

FUNDING

TB-CHAMP is funded by UNITAID as part of the larger BENEFIT-Kids initiative, Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK), Grant number MR/M007340/1 and the South African Medical Research Council (SA MRC, through the SHIP programme). Trial drugs will be supplied by Macleods, India.

AUTHORISATIONS AND APPROVALS

This trial will be submitted for approval by Research Ethics Committees (REC) or Institutional Review Boards (IRB) in South Africa and the UK; and by all required regulatory authorities including the South African Health Products Regulatory Authority (SAHPRA), formerly the South African Medicines Control Council (MCC).

TRIAL REGISTRATION

This trial will be registered with the International Standard Randomized Clinical Trial Number Register Clinical Trials Register (ISRCTN92634082).

SAE REPORTING

Within one working day of becoming aware of an SAE, please securely email a completed Event form to the MRC CTU

tbchamp.mrcctu@ucl.ac.uk

TRIAL ADMINISTRATION

Please direct all queries to the Trial Manager at MRC CTU in the first instance; clinical queries will be passed to the Trial Physician and Protocol Principal Investigators via the Trial Manager.

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SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Short name of Title of Trial	Tuberculosis Child and Adolescent Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)
Long Title of Trial	A phase III cluster-randomised placebo-controlled trial to assess the efficacy of preventive therapy in child and adolescent contacts of multidrug-resistant (MDR) tuberculosis (TB)
Version	V 3.0
Date	9 February 2021
ISRCTN #	ISRCTN92634082
Study Design	Parallel group, 2 arm, cluster randomised, double-blind placebo-controlled TB prevention trial
Type of Participants to be Studied	Children and adolescents (with and without HIV, 0-17 years) who are household contacts of adult MDR-TB index cases
Setting	South Africa (Cape Town, Johannesburg, Klerksdorp, Port Elizabeth, Durban, Pietermaritzburg)
Interventions to be Compared	Levofloxacin (15-20mg/kg, maximum 750mg) to be compared against placebo
Study Hypothesis	24 weeks daily dosing of levofloxacin will protect children and adolescents exposed to MDR-TB from developing TB disease
Primary Outcome Measure(s)	Incident TB disease (confirmed or unconfirmed) including TB death, by 48 weeks post-randomisation
Secondary Outcome Measure(s)	1. TB disease by 72 weeks 2. Mortality (all cause, non-traumatic, and TB related) by 48 and 72 weeks 3. Adverse events grade ≥ 3 that are at least possibly associated to study drug during 24 weeks of treatment 4. Adverse events grade ≥ 3 5. Percentage of levofloxacin or levofloxacin-placebo doses taken by 24-28 weeks 6. Levofloxacin resistant TB disease
Randomisation	Households will be randomised 1:1 to either levofloxacin or placebo taken daily for 24 weeks; all eligible children and adolescents within the household will be treated with the same intervention

Number of Participants to be Studied	1009 children and adolescents from approximately 505 households of adult MDR-TB index case (assuming on average 2 children and adolescents aged <18 years per household)
Duration	72 weeks in total, including treatment for 24 weeks and post-treatment follow-up of 48 weeks
Ancillary Studies/Substudies	Nested economic and qualitative feasibility studies will evaluate the cost, impact and acceptability of the preventive strategy, from the child/family and TB control programme perspectives. Further nested studies will include pharmacokinetic studies, TB diagnostic and biomarker studies and studies assessing the effect of fluoroquinolones on bacterial resistance and on the gut microbiome.
Sponsor	Stellenbosch University, South Africa
Funder	UNITAID, Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK) South African MRC (SHIP Programme)
Principal Investigator	Professor Anneke C. Hesselning

TRIAL SCHEMA

Figure 1. Trial Entry, Cluster-Randomisation and Treatment

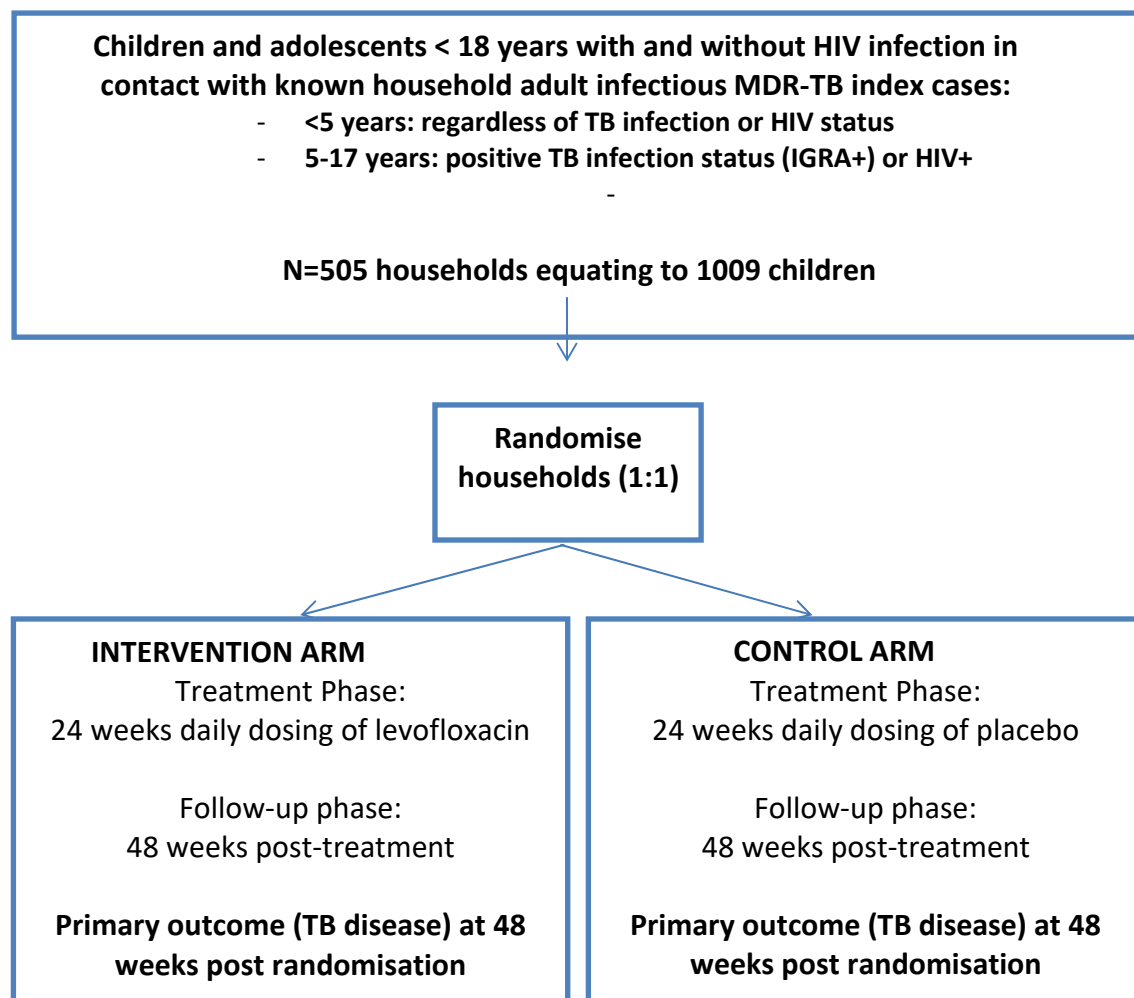


Table. 1. Schedule of Evaluations

	SCR	BL 0	4	8	12	16	24	36	48	72 b	U/S; Early exit/ incident TB	
Symptom screening	•	•	•	•	•	•	•	•	•	•	•	
Medical history	•	•	•	•	•	•	•	•	•	•	•	
Pregnancy test (if female and started menstruating)	•	•										
Clinical examination	•	•	•	•	•	•	•	•	•	•	•	
Chest radiograph	•	#	#	#	•	#	#	#	•	#	#	
Intercurrent TB exposure ^a			•	•	•	•	•	•	•	•	•	
Bacteriological investigation, DST, genotyping (child participants)	#	#	#	#	#	#	#	#	#	#	#	
EQ-5D-Y		•			•		•			•		
Historical TB microbiology data (adult index case; no additional sample collection)	•											
Anthropometrics (height/length & weight, mid-upper arm circumference)	•	•	•	•	•	•	•	•	•	•	#	
IGRA (QFT-Gold Plus)	• (4ml)											
HIV status ((all) HIV negative participants to be tested)		• 0.5 ml							• 0.5 ml			
WHO staging (HIV-positive children/adolescents only)		•							•			
CD4 count (HIV-positive children/adolescents only)		• 0.5 ml					• 0.5 ml		• 0.5 ml	• 0.5 ml		
HIV viral load (HIV-positive children/adolescents only)		• 0.5 ml					• 0.5 ml		• 0.5 ml	• 0.5 ml	#	
Solicited adverse events			•	•	•	•	•				•	
Adherence			•	•	•	•	•				#	
Acceptability and palatability		•	•	•			•					
Outcome (incident TB, mortality)			•	•	•	•	•	•	•	•	•	
Haematology (FBC, differential)		• 0.5 ml		• 0.5 ml							#	
Liver function tests (ALT, BR)		• 0.5 ml		• 0.5 ml		• 0.5 ml	• 0.5 ml				#	

	SCR	BL 0	4	8	12	16	24	36	48	72 ^b	U/S; Early exit/incident TB	
Biomarkers (all)		•		•							•	
Serum, 2.5 ml in red top tube (5-8 x 0.2 ml aliquots)		5ml		5ml							5 ml	
Whole blood 2.5 ml in PaXGene tube (biomarker, diagnostic studies)												
Sub study (Limited to DTTC, only in children <5 years)											•	
Stool (microbiome and AMR)***		•		•		•	•		•		•	
Total blood volumes (HIV-uninfected)	4.0 ml	6.5 ml		6.0 ml		6.0 ml	6.0 ml		0.5 ml	0 ml	5.0 ml	Total (maximum) 39 ml
Total blood volumes (HIV-infected)	4.0 ml	7.5 ml		6.0 ml		6.0 ml	7.0 ml		1.0 ml	1.0 ml	5.0 ml	Total (maximum) 42.5 ml

SCR: Screening; BL: baseline – at randomisation; U/S: unscheduled.

^aIf intercurrent exposure to a documented INH susceptible infectious TB source case, standard TB preventive therapy will be offered;

#based on clinical indication only – TB symptoms at baseline, or at follow-up: new or persistent symptoms, or CXR changes at any time including end point evaluation. Additional indications for repeat CXR include persistent/new symptoms, new TB exposure or previous CXR abnormality.

HIV testing at 48 weeks will be repeated in HIV-negative participants. If the HIV status is already known to be positive at screening, the CD4 count and HIV viral load should be completed at baseline in HIV-infected children. If information is already available (testing completed during the last 12 weeks, routine lab testing results may be used for HIV viral load and CD4 count). ^bThis was previously 96 weeks but was reduced when the protocol was amended to v2.0. Therefore some participants recruited under v1.0 may have reached 96 weeks follow up. For TB microbiological investigation: Gastric aspirates or induced sputum should be completed in children < 5 years of age. In children 5 years and older, expectorated or induced sputum should be completed.

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ABBREVIATIONS

Abbreviation	Expansion
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AFB	Acid-fast bacilli
ALT	Alanine transaminase
AP	Anterior-posterior
AR	Adverse reaction
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area under the (time-concentration) curve
BCG	Bacillus Calmette–Guérin
CDC	United States Centers for Disease Control
CI	Chief Investigator
CI	Confidence Interval
C _{max}	Maximum concentration
C _{min}	Minimum concentration
CNS	Central nervous system
CRF	Case Report Form
CSF	Cerebrospinal fluid
CTU	Clinical Trials Unit
CXR	Chest X-ray
DALY	Disability adjusted life years
DFID	Department for International Development
DOT	Directly Observed Therapy
DST	Drug susceptibility test
DS-TB	Drug-Susceptible Tuberculosis
DTTC	Desmond Tutu TB Centre
ECG	Electrocardiogram
EPTB	Extrapulmonary tuberculosis
ERC	Endpoint Review Committee
EQ-5D	Health-related quality of Life
FDA	(US) Food and Drug Administration
FQN	Fluoroquinolone

Abbreviation	Expansion
GCP	Good Clinical Practice
Hb	Haemoglobin
HHC	Household Contact
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IGRA	Interferon Gamma Release Assay
IMP	Investigational medicinal product
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INH	Isoniazid
IQR	Inter-quartile range
IRB	Institutional Review Board
ISF	Investigator Site File
IPT	Isoniazid Preventive Therapy
ISRCTN	International Standard Randomised Controlled Trial Number
LTBI	Latent TB infection
LFX	Levofloxacin
LYG	Life years gained
<i>M.tb</i>	<i>Mycobacterium tuberculosis</i>
MCC	South African Medicines Control Council
MCV	Mean corpuscular volume
MDR-TB	Multi-drug resistant tuberculosis
MIC	Minimum inhibitory concentration
MXF	Moxifloxacin
MITT	Modified Intention-to-treat
MOP	Manual of Operations
MRC	Medical Research Council
MRC CTU	Medical Research Council Clinical Trials Unit
mSV	Millisievert
NGO	Non-governmental organisation
NICHD	National Institute of Child Health and Human Development
NIH	US National Institutes of Health

Abbreviation	Expansion
NSAID	Non-steroidal anti-inflammatory drug
NTP	National TB Control Programme
PAS	Para aminosalicylic acid
PHRU	Perinatal HIV Research Unit
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PMC	PubMed Central
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
QA	Quality Assurance
QALY	Quality adjusted life years
QC	Quality Control
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee
RIF	Rifampicin
RSI	Reference Safety Information
SA	South Africa
SA MRC	South African Medical Research Council
SA NTP	South African National TB Programme
SAHPRA	South African Health Products Regulatory Authority
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
THINK	Tuberculosis & HIV Investigative Network
T _{max}	Time of Maximum Concentration
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team

Abbreviation	Expansion
TSC	Trial Steering Committee
TST	Tuberculin skin test
UAR	Unexpected adverse reaction
UCL	University College London
ULN	Upper Limit of Normal
VL	Viral load
WBC	Whole blood count
WHO	World Health Organisation
WRHI	Wits Reproductive Health and HIV Institute
XDR	Extensively drug resistant

1 BACKGROUND

1.1 DISEASE SETTING AND CONTEXT OF THIS STUDY

Globally the prevalence of multidrug-resistant (MDR)-TB, defined as *Mycobacterium tuberculosis* (*M.tb*) strains resistant to both rifampicin and isoniazid, and of rifampicin-resistant (RR)-TB is increasing, with an estimated 558 000 cases occurring in 2017.¹ MDR and rifampicin-resistant (MDR/RR)-TB are more difficult to treat than drug-susceptible TB, especially in HIV-positive individuals. This threatens global progress towards the World Health Organization (WHO) targets of the End TB Strategy. Only a small proportion of MDR-TB cases were identified, diagnosed and started on treatment and only 48% of patients enrolled on MDR-TB treatment in 2010 were reported to have had successful outcomes. The Stop TB Partnership Global Plan estimated that between 2011 and 2015 about one million MDR-TB patients would need to be detected and placed on treatment.² Many children with MDR-TB exposure are missed and do not receive contact investigation and clinical care.

With the rollout of rapid molecular diagnostic tools including X-pert MTB/RIF, the number of diagnosed adult MDR-TB cases is increasing, with associated increasing numbers of child and adolescent contacts identified. Conservative assessments suggest that in settings with a high burden of TB there are at least 2 household child contacts for each adult TB index case.^{3,4} Globally, at least a million children are therefore potentially exposed to MDR-TB each year. Young children and HIV-positive individuals^{5,6} are at high risk of progressing to TB disease following *M.tb* exposure and infection,⁷ with *M.tb*-infected infants having a 50% lifetime risk of progressing to TB disease^{8,9} in the absence of appropriate preventive therapy. Of children exposed to *M.tb* who progress to disease, >90% will do so within 12 months while the majority of the remainder will progress in the next 12 months.^{3,8,10} While treatment outcomes for MDR-TB disease in children are good (>80% favourable outcomes with individualised therapy,¹¹ in contrast to poor adult treatment outcomes), the treatment of MDR-TB in children is complex, long (median duration 12 months) and is associated with frequent and significant adverse events including ototoxicity, thyroid toxicity and nausea and vomiting.¹¹⁻¹⁴ Appropriate drugs and child-friendly formulations of second-line TB drugs are limited and interactions between antiretroviral therapy (ART) and TB drugs are common.¹⁵⁻¹⁷ MDR-TB in children is expensive to treat and frequently requires prolonged hospitalisation.^{18,19} Prevention of MDR-TB in children is therefore of paramount importance. The United States Centers for Disease Control (CDC) identified the need for a preventive therapy trial for contacts of MDR-TB in 1992.²⁰ Since then numerous international agencies have also recommended that such a trial should be a global health priority^{16,21-25} but none have been conducted to date, despite the global increase in MDR-TB. WHO therefore specifically does not recommend any specific drug regimen in household contacts of infectious MDR-TB cases.

1.2 EVIDENCE FROM THE LITERATURE

There is robust evidence regarding the efficacy of post-exposure INH preventive therapy to reduce the risk of disease progression in child and adult contacts of drug-susceptible TB.^{26,27}

INH monotherapy (INH, 10-15 mg/kg), given daily for 6 months, is therefore recommended by WHO as preventive therapy in children aged <5 years and children/adolescents living with HIV following exposure to drug-susceptible infectious TB in high-burden settings.^{10,26-29} However, no randomised controlled trials have been carried out to assess the efficacy of MDR-TB preventive therapy.³⁰ A few studies³¹ provide some evidence for the efficacy of MDR-TB preventive therapy. A study from Cape Town described the treatment of 105 children exposed to MDR-TB, in which 2 (5%) of 41 children given preventive therapy for six months with a drug regimen tailored to the drug susceptibility test (DST) results of the index case developed TB, whereas 13 (20%) of 64 children not given any prophylaxis progressed to disease.³ An outbreak investigation, carried out by the CDC in Chuuk, Micronesia, identified 5 MDR-TB cases and 119 infected adult and child contacts. All contacts were offered preventive therapy for 12 months consisting of a fluoroquinolone (FQN) and one other agent. None of the contacts who received the treatment developed TB. However, 28 contacts who did not receive any prophylaxis progressed to disease.³² Recently, in the US, 26 children were given levofloxacin (LFX) and pyrazinamide (PZA) following exposure to their teacher who had MDR-TB; none developed TB disease.³³ A recent systematic review and meta-analysis evaluated all studies of MDR-TB preventive therapy and concluded that there were limited studies and no controlled trials. From the data available, the review did indicate that preventive therapy for MDR-TB was associated with a risk reduction of 90%.⁸⁶ There are a number of studies that suggest that INH alone is not effective as preventive therapy for children exposed to MDR-TB. In a study from Brazil, 188 MDR-TB contacts were identified and found to have TB infection. TB developed in 2 (4%) of 45 contacts who received INH and 13 (9%) of 145 (1.7 per 1000 person-months of contact) who did not receive INH ($p = 0.47$).⁴ A study from Cape Town described 5 child MDR-TB contacts that developed TB disease while on either INH prophylaxis or a combination of INH, PZA and RIF.³⁴ A study from France identified 1 child in contact with an INH mono-resistant index case who developed TB while on prophylaxis with INH.³⁵ International guidelines,^{20,36-39} expert opinion^{40,41} and practice⁴²⁻⁴⁷ are all inconsistent regarding a preventive MDR-TB regimen. Some guidelines advise no treatment,^{36,37} some giving INH at a standard dose, some INH at high dose and others giving two drugs to which the isolate of the index case is susceptible.^{20,48} There is therefore a clear need for high-quality evidence from a trial.

1.3 RATIONALE FOR TRIAL POPULATION

This trial targets the following high-risk groups: firstly, children less than five years of age (regardless of TB infection status). Children less than five years are at the highest risk of progressing to TB disease following infection. From studies that examined the natural history of TB, conducted prior to the chemotherapy era, infants (<12 months) have a 50% risk of progression to disease in the absence of preventive chemotherapy. Children from one to two years have a 20-30% risk and those from three to five a risk of 5%.⁹ However, tests of *M.tb* infection are less reliable in very young children and in children with HIV, given universal BCG vaccination of infants in high-burden TB countries and limited sensitivity of assays in HIV-positive children.^{49,50} For this reason all children less than five years regardless of HIV status will be included in the study, irrespective of the result of their test of *M.tb* infection. Not only are the infection tests less reliable in these patient groups but these children are at the highest risk of disease progression and so most likely to benefit from preventive therapy should it be effective. Tests of TB infection would, however, be completed in this group to allow for sub-group analyses.

In the recent Martinez systematic review and meta-analysis, children with drug-susceptible TB exposure not receiving TB preventive therapy with a positive result for TB infection had significantly higher 2-year cumulative TB incidence than children with a negative test of TB infection, and this incidence was greatest among children below 5 years of age (19.0% [95% CI 8.4-37.4]).⁸⁷ The effectiveness of preventive therapy was 63% (adjusted HR 0.37 [95% CI 0.30-0.47]) among all exposed children, and 91% (adjusted HR 0.09 [0.05-0.15]) among those with a positive test of TB infection. Among all children <5 years of age who developed TB, 83% were diagnosed within 90 days of the baseline visit. This group of children is therefore most likely to benefit from MDR-TB preventive therapy. Furthermore, this trial will target children (HIV-positive and negative) under 5 years of age, regardless of tuberculin skin test (TST) status, to ensure programmatic relevance, since WHO and the South African National TB Programme (SA NTP) do not mandate tests of TB infection prior to initiating TB preventive therapy in children < 5 years of age.

The second high-risk group will include children and adolescents 5-17 years in the household with evidence of TB infection or those living with HIV irrespective of TB infection status. Based on the emerging data from the large Martinez meta-analysis from observational studies, this group of children have a higher risk of disease progression than previously appreciated, which is similar to the risk observed in all children <5 years of age (with and without proof of TB infection). Martinez *et al.* showed that TB incidence is 3-4 times higher in children aged ≥5 years who are IGRA/TST-positive compared to those aged <5 years who are IGRA- and/or TST-negative in household contacts of drug-susceptible TB.⁸⁷ Therefore, older children who are IGRA-positive could potentially be at increased risk of TB progression compared to the cohort currently enrolled into TB-CHAMP, given that only 20% of children <5 years of age in the study to date have been IGRA-positive.

Furthermore, the WHO in their updated 2020 guidelines for TB preventive therapy (TPT) now recommends offering TPT to all child and other household contacts. In children <5 years, TPT should be offered regardless of TB infection status. In children 5 years and older and in adults, TPT should be offered to those with a positive test of TB infection (IGRA or TST) or those living with HIV. No specific regimen is formally recommended for contacts of MDR-TB, given the limited evidence base. South African guidelines for TPT will include all child contacts regardless of age going forward during 2021. The inclusion of this group of children would enhance the generalisability of trial results, while supporting accrual of at-risk children to this trial. Recruitment of older children in the household will offer more benefits for all children in the household and will also improve the recruitment rate of TB-CHAMP, given the challenges to recruit only children < 5 years of age across sites.

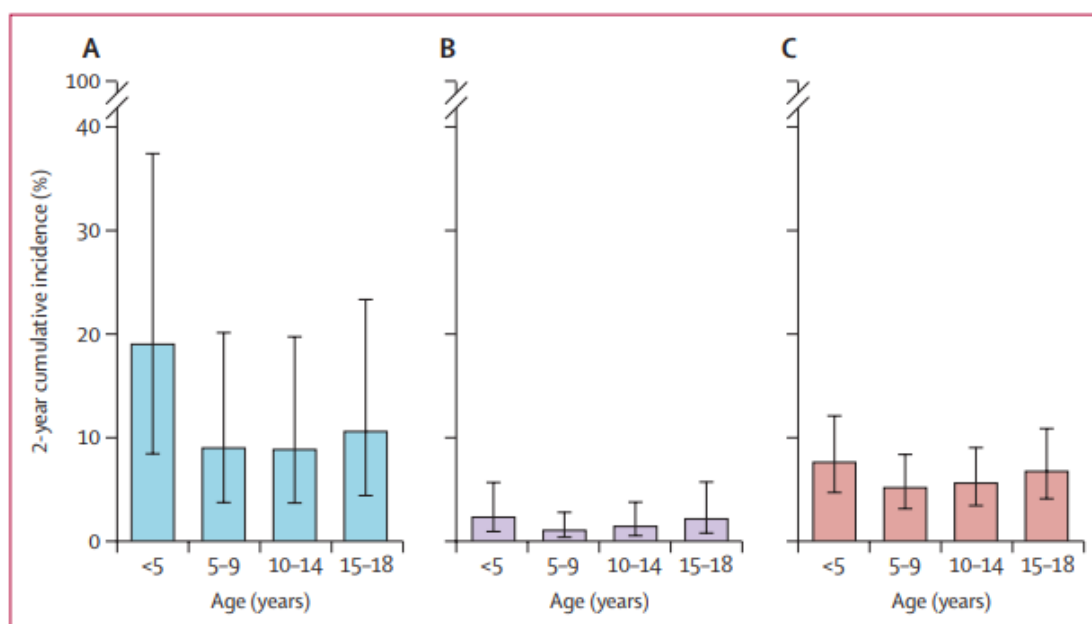


Figure 2: 2-year cumulative incidence of tuberculosis (TB) among children not receiving TB preventive therapy, with positive baseline TST or IGRA results (A), negative baseline TST and/or IGRA results (B), and in all children, including those not tested for TB infection (C) from Martinez *et al.*, 2020.⁸⁷

1.4 RATIONALE FOR CHOICE OF REGIMEN IN INTERVENTION AND CONTROL ARMS

INTERVENTION ARM

Levofloxacin has been chosen as the intervention; the rationale is outlined below. Potential drugs considered for inclusion in the intervention regimen were the first-line TB drugs, the fluoroquinolones, ethionamide, *para*-aminosalicylic acid (PAS), cycloserine, linezolid, clofazimine and novel agents (bedaquiline and delamanid, which have both been recommended for licensure by either the United States Food and Drug Administration [US FDA] or European Medicines Agency [EMA], with bedaquiline licensed in adults in South Africa in 2014.)^{17,53}

Rifampicin (RIF) is unlikely to be efficacious against isolates with *rpoB* gene mutations and high rates of drug resistance to ethambutol and PZA are seen in strains already MDR.^{54,55} In contrast, some limited rationale exists for the use of INH as it would be efficacious in preventing disease if the participant were infected from a (drug-susceptible) index case other than the identified MDR-TB case. Additionally, high-dose INH has potential efficacy against MDR strains with *inhA* mutations, which occur in some settings.⁵⁶ Ethionamide is frequently associated with significant nausea and vomiting and additionally will not likely be efficacious against MDR strains with *inhA* promoter region mutations.⁵⁶ PAS causes profound nausea and diarrhoea and has unclear efficacy. The efficacy of cycloserine is unclear and the drug is associated with significant neuropsychiatric adverse events in adults. Linezolid and clofazimine, while potentially efficacious, do not have sufficient efficacy data and are associated with significant adverse events. Linezolid is expensive at present and also has significant side effects including neurotoxicity.

For bedaquiline, there are currently no pharmacokinetic (PK) or safety data in young children and no paediatric formulation is yet widely available. Delamanid has started phase evaluation in phase I and II trials in older children/adolescents (aged 6-17 years), and it is anticipated that paediatric formulations will become available during the TB-CHAMP trial as well as PK and safety data.

Fluoroquinolones (FQNs) have good efficacy against susceptible and MDR strains of *M.tb in vitro* and are a core component of MDR-TB treatment regimens in both adults and children. In adults, FQN use is associated with successful treatment outcomes, suggesting clinical efficacy.⁵⁷ Traditionally, clinicians have been hesitant to use FQN in children following early animal research demonstrating cartilage damage in juvenile beagles.⁵⁸ However, a significant body of evidence has demonstrated drugs of this class to be safe in children, even for long-term use.^{13,31,59} In a literature review involving over 7000 children, possible FQN-related arthropathy was identified in 10 children, 7 of whom received pefloxacin (an early generation FQN, now not used); symptoms were reversible in all but 1.⁶⁰ In another study of over 6000 children, tendon or joint disorders were seen in <1% and were not more common than with azithromycin.⁶¹ Recently, however, a high proportion of children treated with LFX and PZA for MDR-TB exposure developed adverse events (AE). However, it must be noted that the population included mainly older children and the study may have been affected by recall and ascertainment bias.³³ Reports of an increase in *Clostridium difficile* infection in children following FQN use have also been recently raised.⁶² It is also critical to provide safety data regarding the long-term use of fluoroquinolones for TB prevention in young children, who have a high risk of progressing to TB and severe forms of TB. Careful safety monitoring is therefore of paramount importance in this placebo-trial and is very systematically studied, recorded, analysed and disseminated.

Regarding PK, in a single-dose study of LFX in 85 children in 5 age groups, children <5 years had clearance twice that of adults.⁶³ In an MDR-TB outbreak in Micronesia, children were treated with LFX 5-20 mg/kg/day, and modelled PK data suggested that a dose of 15-20 mg/kg would achieve a drug exposure target of free AUC/MIC > 100.⁶⁴ This has been confirmed in the study described in our pilot data (see **Section 1.4**) conducted by our team in Cape Town.

The prevalence of resistance to FQN in adults and children with MDR-TB even in high-burden TB settings like South Africa is variable at ~ 15%.^{65,66} Recent studies suggest that although moxifloxacin (MFX) has good efficacy against metabolically active mycobacteria, LFX has better activity against mycobacteria in latent phases.⁶⁷ A recent mouse model which evaluated a number of novel preventive therapy regimens in a latent infection model found that LFX, MFX and INH had similar efficacy against drug-susceptible strains of *M.tb*. MFX however has no paediatric formulation, is poorly tolerated in its current formulation due to bitter taste and PK data are lacking. It further appears that the active component of MFX is difficult to taste-mask. Extensive attempts to taste-mask MFX have been unsuccessful to date. LFX, in contrast, is licensed in children, has been widely used to treat paediatric MDR-TB, has known PK parameters, does not interfere with anti-retroviral (ARV) drugs and appears to have low toxicity at current recommended doses for the treatment and prevention of MDR-TB.¹⁷ Paediatric formulation development for LFX is highly feasible and has been accomplished for the purpose of this trial. Simple regimens with fewer drugs are likely to be safer and result in better adherence. Although concerns have been raised regarding the use of a single drug which could lead to the acquisition of resistance in individuals who develop TB disease, this is generally not a concern among children who are well and comprehensively screened for disease at baseline and who are likely to develop paucibacillary disease if they do progress to disease. Resistance has not been shown to develop when INH is used as preventive therapy in child contacts of drug-susceptible TB.^{26,68} Children and adolescents with exposure to an infectious adult with documented MDR-TB plus fluoroquinolone resistance will be excluded from this trial.

Dosing, safety and pharmacokinetics (PK) of LFX in children

South African investigators evaluated the PK and potential cardiac effects of LFX (15mg/kg once daily) in 23 South African children (4 living with HIV) aged 0-8 years treated for MDR-TB. Serum was collected prior to, and at 1, 2, 4, 6 and 8 hours post dose.⁶⁹ Maximum serum concentration (C_{max}), time to C_{max} (t_{max}) and area under the time-concentration curve from 0-8 hours (AUC_{0-8}) were calculated. A 12-lead ECG was done 3 hours post-dose, at the putative t_{max} . The median C_{max} [$\mu\text{g/ml}$], median $AUC_{(0-8)}$ [$\mu\text{g}\cdot\text{h/ml}$] and mean t_{max} [h] for LFX were 6.71 (IQR 4.69-8.06), 29.89 (IQR 23.81-36.39) and 1.44 (SD 0.51), respectively. There was no age effect on PK parameters, but elimination was more rapid than in adults. Therefore, drug exposure was about half of that in adults following a standard oral adult dose of LFX (750mg). No QT_c prolongation (>450ms) occurred.⁷⁰ We have subsequently simulated the optimal LFX dose in children through population PK modelling with R. Savic, (pharmacometrician, UCSF, USA). Presuming a minimum inhibitory concentration (MIC) for LFX of 0.5 mcg/mL,⁷¹ a LFX dose of approximately 20 mg/kg (15 mg/kg in children <2 years of age due to immature renal function) will provide adequate drug exposure. We are currently testing this dose in our target population and have preliminary pharmacometric modelling data in more than 100 children below the age of 7 years.⁷² To date, there has been no demonstrable effect of LFX on QT interval prolongation in children. Of the FQNs, LFX has also been shown to be the safest drug in its class regarding QT interval prolongation, compared to other FQNs currently used for MDR-TB treatment (e.g. MFX).^{72,73}

Furthermore, prior to the main randomisation study, a run-in open-label PK bio-availability study evaluated the LFX exposure in the first 24 children on trial in a single site in Cape

Town, using the newly developed LFX paediatric dispersible tablet (See Sections 1.6 and 10).

CONTROL ARM

The team carefully considered the potential concerns in having no active treatment (placebo) comparison but having INH as the comparator was not deemed to be suitable for the following reasons. Based on very low quality evidence, there is no globally recommended drug regimens to prevent TB in drug-resistant high-risk contacts, as evidenced by the 2018 WHO guidelines.¹ Although it is acknowledged that INH could protect a small proportion of children in the control arm and that providing high-dose INH was recommended by the South African Department of Health (based on expert opinion), it is not implemented in clinical practice in South Africa. High-dose INH may potentially have an effect on preventing MDR-TB, but mainly if associated with TB disease associated with low-level INH resistance (mainly *inhA* mutations). This hypothetical protective effect will however be very dependent on the mutations causing INH resistance, which in most parts of the world is conferred by *katG* gene mutations, which means that the possible effect of INH would differ dramatically by region.

Given the lack of evidence for the efficacy for INH as MDR-TB preventive therapy, the protocol team, after broad scientific and ethical consideration, determined that it would be most appropriate to use no active drug in the control arm. Methodologically, this design optimally answers the question of efficacy of LFX and will likely be more efficient with fewer children required. From an ethical perspective, it also exposes fewer individuals to potential toxicity (which for INH has been demonstrated to be minimal but not non-existent, and which would theoretically be higher given high-dose INH). This is also the trial design used for the completed NIH-funded IMPAACT P1041 trial, which evaluated the efficacy of pre-exposure INH preventive therapy for children living with HIV and children HIV exposed–uninfected.⁷⁴ In the P1041 trial a placebo was used, as no intervention had been proven to be efficacious when used as part of a pre-exposure strategy. In addition, placebo was used in a recent adult INH preventive therapy (IPT) trial, carried out in South African mines.⁷⁵ A controlled trial of an intervention against no drug addresses the simple question of whether the intervention protects children exposed to MDR-TB from developing TB disease. An INH-controlled trial asks a more complicated question, namely, against a regimen of uncertain efficacy, what is the additional benefit of using the intervention, namely LFX? There is therefore the risk, if INH were used in the control arm, that the efficacy of LFX might be unclear. For example, if there is 5% incident TB in the intervention arm and 10% incident TB in the control arm, this could mean that the intervention is not efficacious and no treatment would also have been 10%, or that both intervention and control arms are efficacious and the rate in the no treatment group would have been higher.

More problematic is a null trial result in an INH controlled study, which would be consistent with equal efficacy of INH and LFX for MDR-TB prevention when compared to no treatment and does not answer the question of whether prophylaxis with either LFX or INH is beneficial. By using a trial design with no active treatment in the control arm, we are more likely to be assured of a clear trial outcome.

We also considered whether to use an open-label design. There is added complexity to using placebo and some ethical considerations concerning subjecting children to having to take a tablet that will provide no direct benefit to them. However, the primary trial end

point, although standardised to as great a degree as possible, remains, to some extent, subjective. Many children, in addition to those with bacteriologically confirmed TB, will be diagnosed clinically with TB (i.e. not bacteriologically confirmed) and the study team felt that even if chest X-rays (CXR) are evaluated in a blinded manner and even if a blinded endpoint review committee evaluates the degree of certainty of the TB diagnosis, that there is significant potential for bias in the diagnosis of the end-point. In addition, there is potential for bias in the reporting of adverse events, with families potentially more likely to report side effects if they know that they are taking an active treatment, known to be associated with adverse events. We therefore have decided to use placebo in the control arm of the study, after careful consultation, to support unbiased assessment of endpoints.

In order to ensure the minimum of risk to children in both arms, all children and symptomatic adults in the household will be comprehensively screened for TB disease at baseline; any active TB cases will not be eligible for study participation and will be referred for appropriate care. Children will also be excluded if they have exposure to both an isoniazid drug-susceptible and an MDR index case, as it would not be ethical to withhold treatment that is proven to be efficacious for isoniazid drug-susceptible TB contacts. All children will be closely followed so that if disease develops, it is detected early and treated effectively. The research sites are all closely linked to the local TB programmes, clinics and hospitals and all sites have excellent linkages to routine clinical TB care services.

Children developing any adverse events will be investigated and managed aggressively; arthralgia and diarrhoea will be closely monitored, along with other potential adverse effects.

In summary, TB-CHAMP is currently the only trial globally specifically addressing MDR-TB prevention in children and in adolescents, populations at high risk of developing TB and severe forms of TB. Levofloxacin is now considered a high-priority drug by the WHO in their latest MDR-TB treatment guidelines, and timely trial data using an available safe drug is seen as a high priority for TB prevention. In a recent policy statement on the treatment of TB prevention, the WHO publicly stated their strong recommendation for therapeutic placebo-controlled trials to be conducted in high- risk MDR-TB contacts.¹ The TB-CHAMP trial is strongly supported by the SA NTP and the WHO.

1.5 PILOT DATA

Risk of TB infection, disease and observational use of fluoroquinolone-based MDR-TB preventive therapy in South African children aged 0-5 years: observational data

During 2010-2011 we recruited 228 children under 5 years of age and with and without HIV infection (i.e. identical to our proposed trial population) into a prospective observational cohort at DTTC in Cape Town, South Africa. All children were in household contact with MDR-TB. 45% were TST positive and 6.6% had prevalent TB at enrolment; approximately 4% were HIV-positive.⁷ Consistent with local clinical practice at the time and at this single site (expert opinion), children without TB disease, were given preventive therapy, consisting of INH (15-20mg/kg), ofloxacin (15-20mg/kg) and ethambutol (20-25mg/kg) daily for six months. Children were monitored for clinical outcomes and AEs. Six children (3.2%),

disease-free at baseline, developed TB and 1 child died (not TB-related; probable Sudden Infant Death Syndrome). Poor adherence was associated with poor outcome (rate ratio: 7.50; 95%CI: 1.23-78.7).³¹ Only 4 children were lost to follow-up. Ofloxacin was the only FQN available in the SA NTP at the time. The regimen was well tolerated; 3.2% of children developed grade 3 or higher toxicity over nearly 100 patient-years on treatment. The majority of events were due to inadvertent overdosing, resolving on dosage correction. LFX is now routinely used in South African children (<8 years) in the place of ofloxacin for MDR-TB treatment. As previously described, the concomitant use of INH and ethambutol would offer little additional protective effect, given the high prevalence of resistance to these drugs in MDR-TB isolates, while posing additional risk of toxicity.

1.6 DATA FROM OTHER TRIALS

Levofloxacin safety and pharmacokinetics in children and adolescents

In a prospective pharmacokinetic cohort study, the safety, and tolerability of LFX was assessed in 70 children aged 0-8 years (median age 2.1 years) who routinely received levofloxacin at a dose of 15-20 mg/kg as standard of care for MDR-TB in Cape Town, South Africa. Children were observed for a total duration of 68.5 person-years (median, 11.6 months [interquartile range, 9.2–14.7 months]). There were no grade 3 or 4 or any serious adverse events attributed to LFX, and no adverse event resulted in permanent levofloxacin discontinuation. Specifically, there were only three grade 1 events of arthralgia/arthritis, and no grade 2 or higher musculoskeletal events. The few musculoskeletal complaints (pain, arthralgia) were mild and self-limited. No notable adverse events of hyperactivity or sleep disturbances were noted. With regard to QT prolongation, no child had a Fridericia corrected QT (QTcF) >450 ms, and few had a change >30 ms from pre-dose to 2 hours. We did not observe a relationship between QTcF and LFX concentration. There were no grade 3 or 4 neuropsychiatric events.⁹⁰ In summary, LFX was safe and well tolerated in this group of children.

The V-QUIN trial (ACTRN12616000215426) evaluated 24 weeks of levofloxacin vs. placebo for prevention of TB in TST-positive adults and adolescents with household MDR-TB exposure, in Vietnam, randomized 69 children < 15 years of age, of which 61 were aged 5-14 years, out of a total of 1900 participants, primarily adults. The V-QUIN trial only commenced recruitment of children <15 years near the end of the study, due to a period of observation of the safety of levofloxacin in adult participants. The number of child participants of each age group randomised to levofloxacin or placebo were as follows: <5 years: 8; 5-10 years: 23; 10-17 years: 126 (total children <18 years = 157). All of these participants have completed the treatment period. There were no SAEs reported that were related to the study drug among any children ;;Study drug was well tolerated overall in adults and children, and no grade 3 or 4 events in relation to study drug reported (personal communication, Professor Greg Fox, PI). The trial is expected to disseminate primary results during late 2022 (i.e. after TB-CHAMP is projected to have finished accrual).

Finally, in the run-in study prior to opening TB-CHAMP to randomization, we characterized the pharmacokinetics of the novel 100-mg levofloxacin dispersible formulation in children below 5 years of age with MDR-TB exposure. Twenty-eight children were enrolled. One child was withdrawn before pharmacokinetic sampling, so 27 children contributed to safety data. The median age of children completing pharmacokinetic sampling (n= 24) was 2.1 years (interquartile range, 1.2 to 2.7 years); all were HIV negative, 3 (13%) had a weight-for-age

Z-score of less than -2. The current data were pooled with previously published data from children (n= 109) with MDR-TB receiving adult (250-mg) levofloxacin tablets, using nonlinear mixed-effects modelling. The levofloxacin pharmacokinetic model structure was the same as and the parameter values not significantly different from those of our previous analysis using a routine adult 250 mg levofloxacin, as shown in Table 2, except for the bioavailability of the new dispersible tablets. When the new dispersible tablet was chosen as reference for bioavailability (F 1), the tablets used in the previous study were found to be 41% less bioavailable (ΔOFV 132, 1 extra degree of freedom; P 106). The value of clearance (CL)/F for a typical 12kg 2-year-old child was 2.8 liters/h. After adjusting for full maturation and using allometric scaling to resize to a 70-kg adult, the value became 11.4 liters/h, which was more consistent with scaled values from published adult (CL/F, 8.35 to 9.16 liters/h) and pediatric (CL/F, 11.6).⁸⁸ The formulation was well tolerated and was safe overall. Two participants had three adverse events at least possibly related to levofloxacin, including vomiting (grade 1), difficulty sleeping (grade 1), and anorexia (grade 2). No children had grade 3 or 4 adverse events or any serious adverse events, and none discontinued levofloxacin because of potentially drug-related adverse events. Based on this pharmacokinetic data, further evaluation of the bio-availability and appropriate dosing of the novel 100 mg dispersible formulation is required to ensure that drug exposures are appropriate in children receiving levofloxacin for TB prevention in the TB-CHAMP trial. We therefore will continue the trial with the 250 mg levofloxacin formulation only, which is safe, well tolerated, is feasible to dose, and has well-known pharmacokinetic properties in children. A within-child comparison study of the PK of the 100 mg vs. 250 mg levofloxacin formulations in children is planned independent of the TB-CHAMP trial, through the UNITAID-funded PERFORM trial SAHPRA ref number: 20200321) in South Africa, as part of the BENEFIT-KIDS project.

Levofloxacin in pregnancy

Levofloxacin is routinely used to treat drug-resistant TB in pregnant women. There are limited data available on the pharmacokinetics and safety of levofloxacin for TB during pregnancy. Data from a retrospective cohort study of 108 pregnant South African women routinely treated for MDR-TB, 88 (81%) living with HIV, show that 72 (67%) women had favourable TB treatment outcomes. Ninety-nine (91%) of the 109 babies were born alive. Fifty-eight (54%) women received bedaquiline, and 49 (45%) babies were exposed to bedaquiline *in utero* while about 50% of mothers received levofloxacin. In multivariate analyses, bedaquiline and levofloxacin, drugs often used in combination, were both independently associated with increased risk of low birth weight. Of the 86 infants evaluated at 12 months, 72 (84%) had favourable outcomes. Women living with HIV had a higher risk of an unfavourable pregnancy outcome (uHR 3.35; P = .030). Four infants born alive had congenital anomalies; an umbilical hernia, a ventral septal defect, kyphoscoliosis, and 1 infant had Ehlers-Danlos syndrome. None were attributed to TB medications. There was no association between any TB drug or ART and unfavorable infant outcomes. Maternal HIV status was however associated with unfavourable outcome in infants.⁸⁹

In the TB-CHAMP trial, if any adolescent female were to become pregnant on study, she would be offered the option to continue on the study and on study medication. Additional information is provided in the informed consent form and in the child assent form.

1.7 OBJECTIVES

The main objective of this study is to determine whether LFX, the intervention arm, given

daily for 24 weeks, is efficacious in preventing MDR-TB in high-risk child and adolescent household contacts (HHC) of confirmed infectious adult MDR-TB cases.

Other important questions are:

- Does LFX have acceptable toxicity and tolerability in children and adolescents?
- Is mortality (non-traumatic death) similar in children and adolescents on the 2 study arms?
- What is the adherence to 24 weeks of daily MDR-TB prevention?
- Are there differences in LFX resistance between study arms in children and adolescents developing incident TB?
- Is LFX cost-effective and acceptable to both families and to the TB programme in preventing MDR-TB in child and adolescent household contacts?

2 SELECTION OF SITES/CLINICIANS

This trial will be implemented at well-established sites in South Africa, with high burden of MDR-TB:

1. Desmond Tutu TB Centre, Stellenbosch University (SU), Cape Town (DTTC)
2. Matlosana Perinatal HIV Research Unit, Klerksdorp, Wits Health Consortium (PHRU)
3. Wits Reproductive Health and HIV Institute Shandukani Research Centre (WRHI)
4. Tuberculosis & HIV Investigative Network, Pietermaritzburg and Durban, KwaZulu Natal (THINK)
5. Wits Health Consortium Jose Pearson Hospital, Port Elizabeth (WITS Health)

All sites have extensive research experience in paediatric TB trials and in MDR-TB. These centres have been chosen on the basis of the following criteria:

1. Excellent capacity to identify eligible MDR-TB patients and recruit child contacts, through ongoing adult and paediatric MDR-TB studies
2. Strong linkage to TB services, hospitals and community-based TB clinics and NTPs
3. High burden of MDR-TB
4. Close partnership with local stakeholders. All trial sites have strong collaborative relationships with local TB programmes, NGOs and community partners

Additional centres will be considered should the need arise.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

To participate in the TB-CHAMP trial, investigators and clinical trial sites must fulfil a set of basic criteria defined below.

2.1.1 PI'S QUALIFICATIONS & AGREEMENTS

Each site PI should:

- be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, the IRB, and/or the regulatory authority/authorities
- be thoroughly familiar with the appropriate use of the investigational product(s) as described in the protocol, in the current Investigator Brochure, in the product information and in other information provided by the Sponsor
- be aware of, and should comply with, the principles of ICH GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators at the centre
- permit monitoring and auditing by the Sponsor, and inspection by the

appropriate regulatory authority/authorities

- maintain a delegation log of appropriately-qualified persons to whom the investigator has delegated significant trial-related duties.

- sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 ADEQUATE RESOURCES

Each site PI should:

- should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period

- have sufficient time to properly conduct and complete the trial within the agreed trial period

- have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely

- ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions

2.1.3 CENTRE/SITE ASSESSMENT

Each selected clinical trial centre or site must provide a completed Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the centre is willing and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the centre. In addition and in compliance with the principles of ICH GCP, all centre staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU. The MRC CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site File (ISF) at the site and also at the MRC CTU.

2.2 APPROVAL AND ACTIVATION

On receipt of the above documents at the CTU, written confirmation will be sent to the PI.

The centre/site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority/authorities, which was given favourable opinion by the REC and/or IRB.

The centre/site PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the MRC CTU.

3 SELECTION OF PATIENTS

There will be no exceptions to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed to the TB-CHAMP CTU team prior to attempting to randomise the children from the household. Input provided from the Stellenbosch clinical team will also be sought as needed.

Children will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria, and none of the exclusion criteria, as defined below.

3.1 ADULT INDEX CASE INCLUSION CRITERIA

1. Age ≥ 18 years
2. Bacteriologically confirmed pulmonary TB diagnosed from a sputum sample, having started treatment for MDR-TB within the preceding 6 months*
3. Genotypic or phenotypic resistance to INH and RIF. If only tested by Xpert MTB/RIF or MTB/RIF Ultra or other approved molecular tests e.g. line probe assay, the index case can be included if RIF-resistant, without other confirmed DST; i.e. confirmation of both RIF and INH resistance is not required.
4. Written informed consent from the index case (or a close relative if the index case is deceased prior to the completion of screening)
5. At least 1 household contact below the age of 18 years reported to have been residing in the same household as the adult index case in the previous 6 months

**Assessment may be made, on a case-by-case basis, regarding the risk of the child/adolescent's ongoing exposure if the index case is not adherent to MDR-TB treatment or remains infective. The core trial team should be consulted before enrolment of such children/adolescents.*

3.2 ADULT INDEX CASE EXCLUSION CRITERIA

1. MDR-TB with genotypic or phenotypic resistance to FQN

3.3 CHILD/ADOLESCENT PARTICIPANT INCLUSION CRITERIA

6. Child or adolescent < 18 years who is a household contact of an adult MDR-TB index case (as stated under adult MDR-TB eligibility criteria).
7. Primary residence in the household of the adult MDR-TB index case or any contact resulting in significant exposure of the child (Refer to **Section 3.5** for definition of significant exposure outside the household)
8. Consent from the parent or legal guardian for the child/adolescent for HIV testing
9. Consent obtained from the parent or legal guardian for the child/adolescent to be enrolled
10. Assent obtained from any child/adolescent 7 years or older
11. If ≥ 5 years and < 18 years of age, the child/adolescent must have a positive IGRA test before enrolment unless HIV positive

Note: children < 5 years of age are eligible regardless of IGRA status. All HIV-positive children <18 years of age are eligible regardless of IGRA test status.

3.4 CHILD/ADOLESCENT PARTICIPANT EXCLUSION CRITERIA

1. TB disease at enrolment
2. Currently on INH or a FQN (e.g. LFX, MFX, ofloxacin or ciprofloxacin) for ≥ 14 days. TB preventive therapy may be interrupted provided that the child/adolescent participant is recruited into the study as soon as possible.
3. Treated for TB in the previous 12 months
4. Known concurrent exposure to an INH-susceptible (including RIF mono-resistant) index case
5. Weight below 3.0kg
6. Positive pregnancy test at enrolment. *Note: in females who become pregnant on study, continuation on study will be allowed.*
7. 6 months or less post-partum

3.5 NUMBER OF HOUSEHOLD CONTACTS AND HOUSEHOLDS

Randomisation will be at the household level. A total target of 1009 household contacts (505 per arm) from approximately 505 randomised households will be enrolled. The sample size target, based on contacts enrolled rather than households, is more conservative for ensuring adequate power given some uncertainty and the expected variability in the size of households. The assumptions underlying this sample size are given in **Section 9**.

3.6 SCREENING PROCEDURES AND CONSENT

Consent

Written informed consent will be obtained from adults routinely diagnosed with MDR-TB (termed the “index case”) to collect routine clinical and laboratory TB and HIV data (no intervention will be offered to the enrolled adult index cases). The verbal and written consent process will be conducted in the home language of the adult index or closest relative if the index has deceased (Appendix 3). If an additional MDR-TB index case is identified, the TB episode data on that index case would also be captured, after consent has been obtained from the second index case.

Written informed consent to enter into the trial and be randomised must be obtained from a parent/ legal guardian for child and adolescent participants after explanation of the aims, methods, benefits and potential hazards of the trial and **before** any trial-specific procedures are performed for the trial. Assent will also be necessary for children over 7 years, with assent forms for children 7 years and older (see Appendices 4 and 5). Consent and assent processes will be conducted in the home language of the parent/legal guardian and child/adolescent (see Sample Consent Form; Appendix 2). It must be made completely and unambiguously clear that the parent/legal guardian of the child/adolescent is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their or their child/adolescent’s treatment. Consent must

be re-sought when a child's carer/legal guardian changes. Signed consent and assent forms must be kept by the investigator and documented in the CRF and a copy given to the family.

Identifying the adult MDR-TB index case

Figure 3 shows the participant flow through the study. Adult MDR-TB index cases will be identified at routine NTP TB clinics, hospitals or other (e.g. laboratory-based) surveillance sites or referrals and will be assessed for eligibility as index cases. Adults will be approached at their local clinic, hospital, at home or other convenient location to provide consent for collection of TB episode data and for permission to conduct a home visit to enumerate eligible child and adolescent contacts. All available original sputum microbiological data collected on adult index cases through routine TB services need to be systematically recorded.

If FQN resistance report available or previously documented, this can be used by the team to assess eligibility for the trial. If fluoroquinolone resistance testing was not done, the adult index case is considered eligible.

The study teams at sites will make multiple attempts to contact every eligible adult index case that has been consecutively referred from local routine TB services. This process reduces the possibility that any MDR-TB index cases or subsequent contacts are systemically excluded.

If more than one adult is identified with MDR-TB, all eligible children and adolescents in the household may be recruited. If an additional adult who has INH-susceptible TB is identified in the household or as a close contact, that household would be ineligible and children and adolescents referred for INH preventive therapy, as per local recommended guidelines.

Household assessment

Following the enrolment of an index case, household screening will be conducted in household contacts. This is to identify child and adolescent household contacts who have prevalent TB disease (and who are therefore excluded from trial participation), and to identify child and adolescent household contacts who do not have prevalent TB disease and so are consequently eligible for enrolment into the trial, if they meet the predefined entry criteria. In general, up to six children < 18 years per household may be recruited. The CTU team should be contacted for permission if there are potentially more than 6 eligible children and/or adolescents per household.

The household will be enumerated either in person with a home visit, or at the facility or clinic where the index case has been screened and informed consent signed. The visit will be undertaken and the household and child/adolescent household contacts with significant exposure enumerated. Household characteristics, household prevalent TB (in all children and adult household members) and children's exposure to *M.tb* will be captured using a standard approach.⁷⁶ Households and household contacts (HHC) will be defined using a

standard inclusive definition.⁷⁷ All household members with suggestive symptoms or signs (adults 18 years and older) will be referred for TB investigation and TB/HIV care as appropriate, even though adult household contacts are not eligible for the study.

The index case, if found to be eligible for the trial, will be approached for verbal permission for the research team to approach their household. This is an essential step as the index case's MDR-TB status would be disclosed by doing this. If consent is not given to approach the household for potential enrolment onto TB-CHAMP, all steps will be taken to refer any household contacts for management in routine TB services, as per local standard of care. Caregivers or parents of potential TB-CHAMP participants are then given the option of enrolling their child(ren) onto the study, with formal written informed consent to be obtained at this point.

If FQN resistance is demonstrated in the index case's baseline specimens after enrolment of the participant, the participant will be discontinued from the study treatment and refer for standard of care treatment; however the participant will be followed on study for outcomes. This will be classified as a late exclusion criterion.

Definition of household contact

A household contact is defined as a person who currently lives or lived in the same dwelling unit or plot of land and shares or shared the same housekeeping arrangements as the adult MDR-TB index case, and where there is reported exposure within 6 months prior to the index case starting MDR-TB treatment.

Definition of significant exposure to MDR-TB outside the household:

A child/adolescent who has been in close contact, detected through the trial's household contact investigation, but is not a formal household member, but who has spent frequent or extended time periods during the day with the MDR-TB index case, during the 6 months before the commencement of the current MDR-TB treatment episode, is classified as being significantly exposed. The protocol team should be consulted prior to enrolment of such a child/adolescent participant to confirm eligibility.

Screening children for TB disease

Children and adolescents aged <18 years who were identified as household contacts of the enrolled adult MDR-TB index case during the preceding 6 months will be screened for study entry and eligibility (**Table 1**). Consent for HIV testing will be obtained at screening. TB signs and symptoms will be captured, and chest radiograph done. Anthropometric measures will be completed. Any child/adolescent with suggestive symptoms or signs of intrathoracic or extrathoracic TB disease, or with concerning CXR, will be investigated for TB (including sampling for TB bacteriological testing) and will be referred for TB care as appropriate.

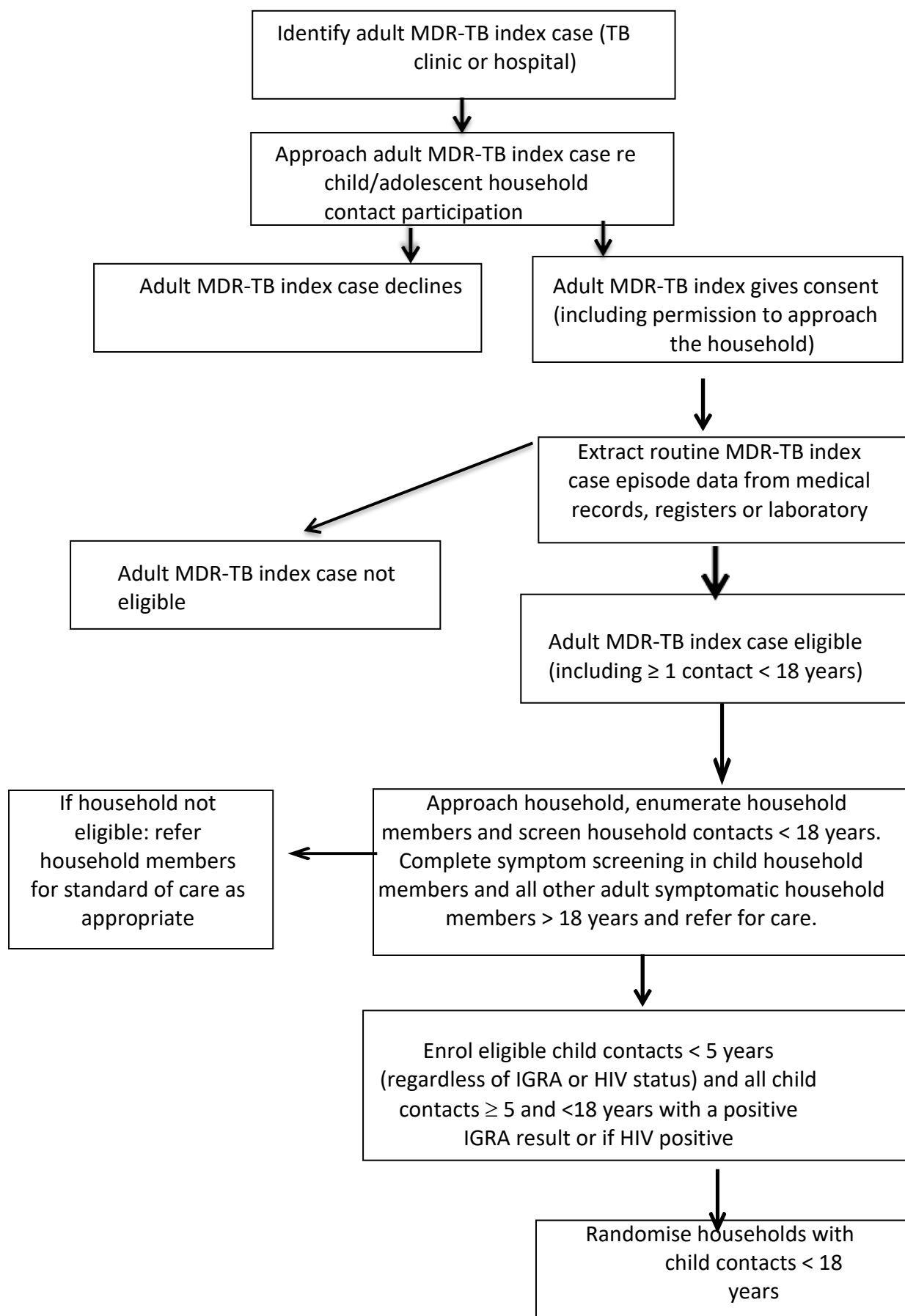
Prevalent TB in child/adolescent HHCs will be defined using standard case definitions (See Appendix 7) using an international case definition for paediatric TB in contact investigation studies, which has been harmonised between several international TB prevention protocols (TB- CHAMP, V-QUIN and the ACTG/IMPAACT Phoenix trials). CXR findings suggestive of intrathoracic (pulmonary) TB are defined in Appendix 7. For children/adolescents with TB disease identified at screening on the basis of historical information as part of routine care (e.g.

single clinical CXR reading, clinical evaluation, bacteriological sampling completed through routine care), historical medical data may be used to define eligibility (i.e. to define prevalent TB). Any child/adolescent with a TB diagnosis prior to randomisation will be excluded from trial participation, regardless of the basis of case confirmation (i.e. even if the case does not meet protocol-defined TB disease case definitions according to the research team).

After consenting to screening, a pregnancy test will be performed in any girls who have reached menses. Girls who have started menses will be advised on how to avoid pregnancy after consultation with the primary caregiver. Preliminary data on the use of levofloxacin during pregnancy is provided in section 1.6. Any female participant who becomes pregnant on the trial will be able to continue with the study drug if they choose to do so, but will be able to withdraw from treatment and continue the clinical follow up only; this will be the participant's choice. If any female becomes pregnant on study, she will be followed for the final pregnancy outcome. At enrollment, any female participant found to be pregnant or 6 months or less post-partum will not be eligible for the trial due the potential for breastfeeding and unknown transfer of levofloxacin via breastfeeding.

See **Appendices 1 and 2** for Patient Information Sheet and Consent and Assent templates. See **Section 6** for the full list of assessments at screening.

Figure 3. Overview of participant flow



4 ENROLMENT AND RANDOMISATION

4.1 ENROLMENT AND RANDOMISATION VISIT

Informed consent will follow a multi-stage process as an important pre-requisite to randomisation.

Adult MDR-TB index cases (adults with MDR-TB) will be consented to determine personal and household characteristics and obtain TB episode data. A close relative may provide informed consent if the adult MDR-TB index case is deceased.

Child/adolescent household contacts will be approached and written consent obtained from a parent or legal guardian if eligibility criteria are met.

If the child is 7 years old or older, they will also be required to sign assent including once they reach this age

Before the household is randomised and treatment is allocated to the participant, their eligibility will be confirmed during the enrolment visit, including the results of screening testing related to TB disease status, age, and predefined safety parameters. For all children 5 years and older and younger than 18 years, either the child/adolescent must be determined to be living with HIV or must have a positive IGRA test before enrolment. Late enrolments (within a window of 14 days) after randomisation of the household will be allowed in consultation with the protocol team. Other child/adolescent contacts in the household who are eligible may be enrolled in the meantime until results of screening are available (i.e. all children in the same household do not need to be enrolled at the same time).

A pregnancy test will be performed if the participant is female and has started menstruating. A negative result will need to be obtained before the participant can be enrolled onto the trial. Any female who is six months or less post-partum will be ineligible for the trial due to the potential for breastfeeding.

See **Section 6** and **Schedule of Evaluations (Table 1)** for the full list of assessments at enrolment.

If any child/adolescent household contact is eligible and consent (+/- assent) has been obtained, and the household is randomised, the site pharmacist will prepare the treatment regimen (according to the study identifier allocation list) for all child/adolescent participants enrolled within that household. All enrolled household contacts in a household consenting to participate will be allocated to the same study arm. The participation of other eligible children/adolescents in the same household is not mandatory.

Enrolment of children/adolescents and randomisation of households into the study will be via a centralised web-based system at the CTU. Site staff with enrolment privileges will confirm participant eligibility through the secure web-based randomisation system.

Randomisation will be stratified by centre, and households will be randomised 1:1 to either levofloxacin (LFX) or levofloxacin-placebo (see **sections 4.2 and 9.1** for more details).

4.2 RANDOMISATION PRACTICALITIES

Randomisation by household allows for ease of drug administration, protection from bias through contamination (intentional or unintentional) and is perceived as culturally acceptable in the study setting, South Africa. Including all eligible child/adolescent household members, rather than a single individual, allows for greater efficiency of resources since costs are dominated by identifying the adult index case; the marginal additional cost of enrolling additional HHCs within a household is low.

The randomisation code will be prepared at the MRC CTU, under the supervision of the Trial Statistician, by an individual that is not involved in the day to day running of TB-CHAMP. The randomisation list which links the trial number unique to each participant to one of the two trial allocations will also be prepared by this individual at the MRC CTU under the supervision of the Trial Statistician.

A file of the randomisation list in which the study products are identified will be kept in an electronically secure location at MRC CTU, with offsite back-up. A hard copy of the link between this number and the product name will also be held securely at MRC CTU. The randomisation code will be held only by the unblinded Trial Statistician(s), authorised database systems staff and by those authorised persons who label and pack the trial supplies. No member of staff other than the unblinded Trial Statistician(s) will have access to the list or code until the analyses are complete and all decisions about relationship of events to study product final. The duty programmer/unblinded statistician(s) for CTU will be able to access the list and code for the purposes of unblinding in the unlikely event that this is required (see **Section 5.5**) according to CTU trial specific procedures.

4.3 CO-ENROLMENT GUIDELINES

Participants will not ordinarily be permitted to participate in any other clinical intervention trial while on the TB-CHAMP trial. Participation in other studies that do not involve an intervention (for example diagnostic, biomarker, epidemiological studies in addition to planned TB-CHAMP sub studies), may be acceptable but should first be discussed with the TB-CHAMP Trial Management group (TMG). The TMG will consider co-enrolment of participants into other trials where the interventions do not conflict with the TB-CHAMP objectives on a case-by-case basis, and after review of the study procedures. Referral may be made from the TB-CHAMP team, once a TB end point has been reached, to other therapeutic TB trials in children.

4.4 GUIDANCE FOR RE-ENROLMENT OF CHILD PARTICIPANTS

Certain participants will be eligible for re-enrolment onto TB-CHAMP. The participants must have completed the entire trial treatment period but not necessarily all follow-up visits and must have been newly exposed to bacteriologically confirmed MDR-TB without fluoroquinolone resistance. Sites must first contact MRC CTU via email before undertaking any screening or re-enrolment procedures in these cases. The potential participants will be discussed on an individual basis with the TMG and written approval must be obtained before

the child is eligible for randomization. The site must review all adverse events to ensure the child has not had any adverse reactions to study treatment and confirm they did not develop TB whilst on the study. The participant must still meet all the inclusion and exclusion criteria as stated in section 3.1 and 3.2.

5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

All children/adolescents within a household who are recruited to the study will be allocated to the same arm of the study. Medications will be given as film-coated or scored tablets, dosed by pragmatic weight-bands (**Table 2**), as commonly done for children with TB in NTPs, and for antiretroviral therapy (ART). Nested economic and qualitative feasibility studies will evaluate the cost, impact and acceptability of the LFX preventive strategy, from the child/family and TB control programme perspectives (**Section 10**). All children/adolescents will be routinely tested for HIV. Children/adolescents living with HIV will be given ART according to national guidelines. Participants living with HIV not currently on ART will be immediately referred for ART as per local guidelines. All children/adolescents diagnosed with prevalent and incident TB will be referred for routine TB treatment, based on local standard of care.

Table 2. Weight bands for levofloxacin (250 mg tablets) and placebo

Weight bands (kg)		Levofloxacin 250	Placebo 250
3	4.9	0.25	0.25
5	6.9	0.5	0.5
7	9.9	0.5	0.5
10	11.9	1	1
12	15.9	1	1
16	19.9	1.5	1.5
20	24.9	1.5	1.5
25	29.9	2	2
30	30.9	2.5	2.5
≥ 40		3	3

Dose modifications should be made based on the child/adolescent's weight and dose adjustments made as required, typically on a monthly basis. This may lead to a change in number of tablets a participant receives compared to the previous weeks. The participant's weight should be documented on the TB-CHAMP Prescription chart to enable verification of the correct dose. Dose reductions for children/adolescents who **lose weight** should be made at the second consecutive visit in order to confirm genuine weight loss rather than a fluctuation. This is to avoid too many dose changes based on (often mild) fluctuations in weight across the weight bands. If the child/adolescent continues to lose weight or not gain weight appropriately, investigations on for TB and comorbidities should be undertaken.

5.2 ARM A - INTERVENTION

Levofloxacin 15-20 mg/kg (max 750mg) per day, once-daily, for 24 weeks.

The 250 mg levofloxacin tablet is manufactured by Macleods, India (Table 2).

5.2.1 PRODUCTS

LFX 250 mg tablet, maximum 750 mg daily, dosed using a weight-banding approach. LFX 250 mg is stable for 24 months at 25°C/60% relative humidity (RH), for 6 months at 40°C/75%. Store at 25°C (77°F); excursions permitted at 15-30°C (33-86°F).

LFX 250 mg tablets from Macleods are approved in South Africa. Levofloxacin is a WHO Prequalified medicinal product (see <http://apps.who.int/prequal/query/ProductRegistry.aspx>), which means that its quality is assured by an expert panel, based on information submitted by the manufacturer and inspection of the corresponding manufacturing sites (Appendix 8).

LFX 250 mg tablets and placebo will be labeled according to guidelines for clinical trials (Good Manufacturing Practice guidelines, Appendix 8).

5.2.2 TREATMENT SCHEDULE

Once daily LFX dosing, taken with or without food, for 24 weeks.

5.2.3 DISPENSING

Dispensing will be done centrally by the site pharmacist. Medication (or placebo) will be provided to child participants by study personnel, who may dispense study drug, at scheduled study visits, typically every 4 weeks, during the 24 weeks on study drug.

5.2.4 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

Treatment interruptions of up to 4 total weeks will be allowed with an additional 4 weeks added to the treatment, resulting in a total treatment duration of at most 28 weeks.

Individual missing doses will be documented with the aim being to ensure that all participants receive at least 80% (134/168) of all doses prescribed, considered as adequate adherence. However, only 4 weeks will be allowed to make up for missed doses after the 24-week treatment period has ended. If by 24 weeks, 134 doses have not been given, treatment should be extended by up to 4 weeks to get to the 134 doses. If >4 weeks is required to get to the 134 doses, treatment will not be extended beyond 4 weeks. The rationale is to have a 6 month pragmatic strategy. At the week 24 visit, the adherence assessment should be made by the study clinician, the total number of doses estimated to have been taken reported on the relevant CRF, and a decision made as to whether to extend treatment by an additional 4 weeks.

Stopping Drug Early

Discontinuation criteria are considered in **Section 5.6**

5.2.5 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

Pill counts will be completed by the clinical study personnel. Unused drug will be returned to the trial pharmacist. The site pharmacist will be required to maintain complete records of all study products received and subsequently dispensed. The site pharmacist must follow the instructions in the Pharmacy Guidelines and Instructions for the destruction of unused study products (Refer to the Manual of Operations; MOP, including the pharmacy plan).

5.2.6 COMPLIANCE & ADHERENCE

Study drug will be administered daily by parents/caregivers with treatment adherence support provided. Adherence to LFX will be assessed at clinic appointments and at home visits. Participants will receive adherence support from site personnel, community-based treatment (DOT) supporters or other trained local healthcare workers, as relevant. Adherence will be verified through pill counts and daily TB treatment cards.

5.3 ARM B - PLACEBO

LFX-placebo 15-20 mg/kg (max 750mg) per day, once-daily, for 24 weeks.

5.3.1 PRODUCTS

LFX-placebo 250 mg tablet, maximum 750 mg daily, dosed using a weight-banding approach.

LFX-placebos are manufactured by Macleods and are exactly similar in content (apart from the presence of levofloxacin and some inactive ingredients) to the active drug. See Appendix 8 for further information on the quality of this drug.

Placebo tablets will be labeled according to guidelines for clinical trials (Good Manufacturing Practice guidelines, Appendix 8.)

5.3.2 TREATMENT SCHEDULE

As per section 5.2.2.

5.3.3 DISPENSING

Refer to section 5.2.3

5.3.4 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS Stopping Drug Early

Refer to section 5.6

5.3.5 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

See under Section 5.2.5

5.3.6 COMPLIANCE & ADHERENCE

See under section 5.2.6

5.4 OVERDOSE OF TRIAL MEDICATION

Since neuropsychiatric symptoms have very rarely been reported in the case of paediatric fluoroquinolone overdosing, and other adverse effects are possible, study drug may be discontinued in the case of reported or suspected overdosing, based on the clinical assessment and judgement and the presence of reported or verified adverse effects. See section 7.1.5 for details on drug toxicity and its management.

5.5 UNBLINDING

Whilst it is not anticipated that unblinding will be necessary, a procedure is in place for unblinding through the MRC CTU. If a clinical investigator associated with the study or responsible for the care of a participant considers that knowing the allocation is essential for medical management then they should follow the instructions in the TB-CHAMP Unblinding Procedure and contact the overall PI and Trial Physician or their deputy (details provided on the answer phone message out of office hours) through the following contact information. Any general questions can be emailed to the TB-CHAMP Trial team: tbchamp.mrcctu@ucl.ac.uk. In an emergency during office hours please email the TBCHAMP overall PI: annekeh@sun.ac.za or Phone 0027 82 3001149 (or delegate). +44 (0)20 7670- 4727 or emailing TBCHAMPDATA.MRCCTU@ucl.ac.uk.

IMPORTANT: Unblinding the allocated treatment group should be kept confidential and restricted to the managing clinician(s) responsible for the case

5.6 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, parents/caregivers of child/adolescent participants are consenting to trial treatment, trial follow-up and data collection. However, an individual patient may stop treatment early or be stopped early for any of the following reasons:

- Progression to TB disease (as defined in **Section 6**) during the trial
- Unacceptable toxicity or an adverse event occurs
- Intercurrent illness that prevents further treatment
- Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion
- Inadequate adherence to the protocol treatment in the judgement of the treating physician
- Withdrawal of consent for treatment by the child/adolescent's parent or legal guardian
- Withdrawal of assent for treatment by the child/adolescent
- Relocation to a remote geographic area
- A diagnosis of a new infectious adult TB case in the same household with drug-susceptible TB
- Any suspicion of clinically significant fluoroquinolone related toxicity

As the patient's participation in the trial is entirely voluntary, their parent/legal guardian may choose for them to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although the parent/legal guardian is not required to give a reason for discontinuing their child/adolescent's trial treatment, a reasonable effort should be made to establish this reason while fully respecting the child/adolescent's rights.

5.6.1 EVALUATIONS FOR RANDOMISED OR ENROLLED PARTICIPANTS WHO DO NOT START STUDY TREATMENT

Eligible contacts who do not start treatment but who have been enrolled will be followed for the entire study duration according to the schedule of events.

5.6.2 PREMATURE TREATMENT DISCONTINUATION EVALUATIONS

Participants who prematurely discontinue study treatment will continue to be followed on study, off study treatment for the remainder of the study follow-up, according to the schedule of events.

5.6.3 PREMATURE STUDY DISCONTINUATION EVALUATIONS

Participants who prematurely discontinue from the study will have the study discontinuation evaluations performed prior to being taken off the study.

Participants should remain in the trial for the purpose of follow-up and data analysis (unless the parent/guardian withdraws their consent from all stages of the trial). If a participant is withdrawn from follow-up, refer to **Section 6.6**.

Data will be kept and included for patients who stop follow-up early.

5.7 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

All unused study medication should be returned to the site's trial pharmacist and eventually to the central coordinating pharmacist.

5.8 COMPLIANCE & ADHERENCE

Study drug will be administered/monitored daily by parents/caregivers and treatment adherence support will be provided at study visits or between visits as required. Adherence to TB preventive treatment will be assessed at study clinic appointments and at home visits. Treatment will be supported by site personnel, community-based treatment (DOTS) supporters or other relevant local healthcare workers. Adherence will be verified through pill counts and reported adherence (treatment cards) at each study visit. Home visits will be undertaken to support adherence as needed.

5.9 TREATMENT DATA COLLECTION

Treatment data will be collected from daily TB medication cards ("TB treatment cards,") similar to routine NTP TB treatment cards used for IPT in children, which will be developed for the trial and pill counts.

5.10 NON-TRIAL TREATMENT

Whenever a concomitant medication or study medication is initiated or a dose changed, investigators must review the concomitant medications and study medications' most recent package insert, Investigator's Brochure, or updated information to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the updated ACTG Drug Interactions Database located at: http://tdm.pharm.buffalo.edu/home/di_search/Search.

Refer to **Section 7** for potential drug interactions and to Appendix 8 for toxicity management.

6 ASSESSMENTS & FOLLOW-UP

All clinical and laboratory information required by this protocol is to be present in the participant folder. All stated evaluations are to be recorded on CRFs and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event as outlined in Section 7.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the revised Division of AIDS (DAIDS) adverse grading for the adverse events (DAIDS July 2017, version 2.1). [<https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf>].

Participants will be followed for a total of 72 weeks. Follow up will evaluate incident TB, all-cause mortality, adherence to the trial drugs, and toxicity.

Trial visit schedules will be prepared for each participant at randomisation, and participants should be followed on the same schedule even if their trial medication is discontinued. The target dates for trial visits are determined by the date of randomisation and are not affected by subsequent events. The schedule generated after randomisation defines visit dates (with windows) necessary for data collection, but the participant may be seen more frequently for clinical care if needed.

Participants should attend on the scheduled day whenever possible, unless agreed in advance with the clinical research team/site. The site may choose to re-schedule visits to allow for public holidays or other unavoidable circumstances that affect the scheduled visit date. Scheduled assessments should be carried out within +/- 7 days of the scheduled visit in the first 24 weeks, and +/-14 days thereafter.

During the treatment period, if participants are unable to attend on the day, every effort should be made to complete the visit as close as possible to the scheduled date. If a scheduled visit is missed without notice, then the research team should try to contact the participant by phone or by home visit. If a participant is more than 7 days late for a scheduled study visit (during the treatment period and with consideration of the allowed window period), an additional visit should be performed as soon as possible, including the appropriate assessments that were specified in the trial schedule for the visit week that was missed.

Additional study visits may need to be arranged, for example, if the child/adolescent develops potential drug toxicity or other clinical events. These visits may be recorded as “unscheduled visits”. Some routine assessments or other clinically relevant tests as for a standard clinic visit may also be performed as clinically indicated. Other laboratory tests will be performed as clinically indicated.

Pregnancy tests will be done at any follow-up visit if pregnancy is suspected. If a participant becomes pregnant on the trial, they will be allowed to continue if they choose to do so, and the pregnancy will also be followed until the final pregnancy outcome has been determined. If they choose not to receive study medication, they will still be able continue to be followed on study. In the case of a positive pregnancy test, MRC CTU at UCL should be notified and reporting should be done as per local regulatory guidelines (see Section 6.9).

6.1 SCHEDULE OF EVALUATIONS

All participants will be seen at screening, enrolment (randomization/baseline, week 0) and then at weeks 4, 8, 12, 16, 24, 36, 48 and finally at week 72,* when they will exit the trial. A maximum of six weeks will be permitted between screening and enrolment to allow for the exclusion of TB disease in child/adolescent contacts and for families to consider participation in the trial. For the majority of families, however, it is anticipated that screening and enrolment will occur at the same time, as children/adolescents should be started on treatment (or placebo) as soon as possible. See Schedule of Evaluations (**Table 1**).

At each study visit the following will be undertaken:

- Administration of a symptom checklist by a nurse to detect intercurrent illness, new TB exposure, adverse events to trial drugs (and other medications, including ART, if applicable). The severity and likely relationship of any adverse events to individual medications will be documented by a doctor, who will complete the clinical assessment. If TB is suspected at any stage, a doctor should also evaluate the participant clinically.
- Medical history since the last visit including adverse reactions to trial drugs (and other medications, including ART, if applicable), signs and symptoms of TB, HIV disease (if applicable) with WHO stage, and any events requiring hospitalisation
- Weight, height/length, and mid-upper arm circumference
- Changes in TB, ART and other concomitant medications
- Inpatient and outpatient attendances should be recorded on CRFs, both with appropriate laboratory forms completed to document relevant test results
- Assessment of adherence to trial drugs (and ART if applicable) by pill counts, treatment card and nurse-administered questionnaire

In addition, the following will be undertaken at the stated time points:

- A chest X-ray (CXR) in two projections, posterior-anterior (PA) or anterior-posterior (AP; in young children) and lateral, should be performed at screening. Lateral CXR is always required. Children with abnormal CXR or suggestive symptoms will have TB bacteriological investigations completed. A CXR will be repeated at week 12 and week 48 and if clinically indicated, at other study visits. For CXR features suggestive of TB, refer to Appendix 7.
- Interferon-Gamma Release Assay (IGRA) will be performed for all patients at screening/enrolment, with participants aged over 5 and below 18 years only being eligible for the trial with a positive result or if HIV-positive. IGRA tests can also be performed at any point throughout the trial if TB is suspected in conjunction with other TB investigations.
- Pregnancy test at baseline for any female participants who have begun menstruation.
- For females who begin menstruation during the trial, pregnancy tests will be undertaken as well as counselling relating to pregnancy testing if deemed clinically relevant.
- For TB microbiological testing, gastric aspirates or induced sputum should be done in children < 5 years of age. In children 5 years and older or who can expectorate spontaneously, expectorated sputum or induced sputum, should be done.

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- Haematology at baseline and then at week 8, and, if clinically indicated, at additional time points.
 - Lymphocyte subsets and viral load samples for children with HIV at baseline, week 24, week 48 and week 72
 - Whole blood (PaxGene tubes) and serum stored for biomarker and diagnostic sub studies will be taken with each blood draw (baseline and then at week 8, and upon reaching a TB end point or at early trial exit.
 - Stool will be collected (subset of participants under 5 years of age only, and at the DTTC site only; nested sub study), at baseline, week 8, 16, 24, week 48 and upon reaching a TB end point or at early trial exit.
 - EQ-5D-Y at the baseline visit, at weeks 12, 24 and 72. The EQ-5D-Y descriptive system comprises the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3 levels: no problems, some problems and a lot of problems.
 - At baseline and at week 48, HIV testing will be repeated in all HIV-negative participants with appropriate counselling and consent. Participants diagnosed with HIV will be managed as per national South African guidelines, which recommend immediate initiation of ART.

If a new TB exposure is recorded, in addition to the scheduled assessments, a CXR in two projections, AP and lateral, should be performed if a recent CXR is not available (in the last 2 weeks). If the new TB exposure is identified to be due to a TB source cases with isoniazid-susceptible TB, the participant will be discontinued from study drug and referred for IPT, as per standard of care. These participants will continue to be followed in the study and their data will still be included in statistical analyses.

If at any point the participant develops signs or symptoms suggestive of TB disease (**Appendix 7**), in addition to the history and full clinical assessment, the following should be performed (see Early Exit/Incident TB in the Trial Assessment Schedule **Table 1**)

- CXR: AP and lateral.
- Bacteriological investigation, including:
 - If PTB suspected: at least two good quality respiratory samples (expectorated/induced sputum in older children/adolescents or gastric aspirate or induced sputum in younger children), submitted to central trial laboratory.
 - If EPTB suspected: two respiratory samples (expectorated/induced sputum or gastric aspirate) submitted to central trial laboratory (BARC). Additional samples such as fine needle aspiration biopsy or other fluid or tissue samples could be collected by the routine health care system and sent to NHLS. However, if these specimens are culture positive, the TB isolate must be sent to the central trial laboratory (BARC).
 - All samples will be tested with smear microscopy, Xpert MTB/RIF Ultra and MTB culture.
 - DST (first-and second-line DST) and genotyping will be done on *M.tb* culture-positive samples. Isolates will be stored for future use including whole genome sequencing.
- The type of sample / method of collection for TB microbiological investigation will depend on participant's age and clinical presentation (see Manual of

Operations and TB lab guidance).

- Adherence assessment, acceptability questionnaire and EQ-5D-Y questionnaire
- Whole blood (PaxGene) and serum stored for biomarker and diagnostic sub studies (all participant at all sites)
- Stool obtained (subset of participants, (single site only)).

NB: All TB end points microbiological samples (at least 2 good quality gastric aspirates/sputum/induced sputum) must be processed by the central laboratory to ensure that testing is consistent and results are comparable across the sites. If samples were inadvertently collected by the routine health care system and sent to NHLS, culture results must be followed closely and if found to be culture positive, the clinical team must ensure that mycobacterial isolates are sent to the central trial laboratory. In addition, other clinically relevant samples e.g. fine needle aspirates of peripheral lymph nodes, should be obtained as per local standard of care and sent to the routine microbiology laboratory (NHLS).

Case summaries will be completed for all end points (incident TB). Prevalent and incident TB disease in child/adolescent household contacts will be classified using a standard international case definition for paediatric TB studies {Appendix 7 which defines TB as (bacteriologically) confirmed, unconfirmed and unlikely TB}. In addition we will also use MDR-TB consensus case definitions for clinical research in children.^{78,79} An end point review committee (ERC) blinded to study arm, will adjudicate all incident TB endpoints and cause of death. TB disease severity will be classified in a standard manner.⁸⁰ The ERC will also review and adjudicate all TB and other deaths. An ERC charter describes the roles and function of the ERC.

Safety assessments at each visit during the 24-28 weeks on study drug (or placebo) will include symptoms, signs, liver function and full blood count. All clinical and laboratory adverse events will be recorded, classified and reported using DAIDS criteria (see at <https://rsc.tech-res.com//clinical-research-sites/safety-reporting/daids-grading-tables>), with expedited reporting where appropriate.

All hospital admissions and SAEs will be recorded. All TB cases detected will be referred for treatment to local treatment centres, in consultation with the local TB program and routine local clinical care teams.

At each visit, drugs will be dispensed to last until the next clinic visit. Alterations to prescribed doses and prescriptions of any concurrent medications, including ART, should be recorded on the CRF. Doses should be checked at every visit and adjusted for weight as appropriate.

PROCEDURES FOR ASSESSING EFFICACY

Outcome evaluation

The primary efficacy outcome is incident TB disease (confirmed and unconfirmed TB) which would include TB deaths by 48 weeks following randomisation, reportable on an event form.

Incident TB (primary end point) and cause of death will be adjudicated by an independent

Endpoint Review Committee (ERC) blinded to treatment allocation, based on all available clinical, radiological microbiological, drug susceptibility testing and molecular data using the standard international consensus case definitions. The ERC will have access to CXR images and CXR reports from the site clinicians and the central dual blinded expert CXR reading. All potential efficacy outcomes from post-enrolment through the 72 week visit will be reported and reviewed by ERC. TB end points should be captured on the appropriate CRFs and should be reported within one working day as a notable event. Please also refer to the MOP and relevant data capture forms for TB events.

Incident TB

Child/adolescent HHCs will be evaluated to exclude prevalent TB disease at the time of screening. If TB disease arises at any time after the date of randomisation, it will be defined as 'incident' TB. All household contacts with radiological or clinical evidence of pulmonary or extra-pulmonary TB will be referred for routine evaluation in accordance with prescribed local protocols and local standard of care. Assessment of the rate of incident TB after randomisation will be used to assess treatment efficacy in intention to treat analysis. NTP registries (e.g. ert.net, edr.web, TB clinic and hospital registers) will be searched to determine outcomes among individuals lost to follow-up and any potential missed TB cases, including potential TB deaths. In a participant who was lost to follow-up during the trial and where no TB episode has been identified from any source of data, the participant would be classified as lost to follow-up to the trial, and the last date the patient was seen taken as the last observation, for analysis purposes.

Definitions of TB

It is important to have consistency in reporting for paediatric incident TB within studies and as far as possible between studies, for purposes of valid comparison and possible future meta-analysis.

While the clinical, non-bacteriologically-confirmed definitions have uncertainty, it should be emphasized that these definitions are being used to strengthen consistency of reporting, not to inform clinical treatment decisions. These definitions are therefore for the purpose of classification of study endpoints. Decisions to treat for TB (or not) will be made on an individual patient basis. There are various factors that will influence treatment decisions that cannot be classified prospectively – for example, duration of symptoms, response of symptoms to other interventions, severity of illness (i.e. influencing urgency of referral and management), perceived risk (e.g. immune status or age), identification of other index cases (e.g. with DS-TB) opportunity for follow-up and review prior to decision to treat – but which can be used retrospectively for research protocol classification purposes.

The updated revised National Institutes of Health (NIH) case definitions⁷⁹ were specifically designed for diagnostic assessment studies of intrathoracic TB in children. The entry point for such studies would usually be children with symptoms suggestive of intrathoracic TB that presented to health services. Note that in MDR-TB contact studies, there are important differences to consider:

The scope of the clinical case definitions focuses on intrathoracic tuberculosis in children presenting with symptoms. However, there was consensus that extrathoracic tuberculosis,

especially for young children, also needed to be considered.

Entry criteria into tuberculosis diagnostic studies can include children with compatible symptoms and signs of any duration.

- The “clinical signs/symptoms suggestive of tuberculosis” and “interpretation of chest X-ray” for classification of children in tuberculosis diagnostic studies remain unchanged. Children with suspected tuberculosis are followed and reviewed following enrollment in diagnostic evaluation studies, and so the duration and resolution of clinical features can be determined and well defined for purposes of categorization within clinical case definitions.
- Tuberculosis exposure: The period of time used to document tuberculosis exposure prior to enrollment has been shortened from 24 months to 12 months,
- The case definition of “confirmed tuberculosis” now includes a positive WHO-endorsed nucleic acid amplification test (e.g., Xpert MTB/RIF) in addition to culture confirmation using
- a valid respiratory specimen for microbiologic examination, irrespective of the culture result.
- The case definitions for reporting were narrowed from 5 to 3 groups:
- The case definitions “probable tuberculosis” and “possible tuberculosis” are merged into a single case definition of “unconfirmed tuberculosis.”
- The case definitions of “unlikely tuberculosis” and “not tuberculosis” are merged into a single case definition of “unlikely tuberculosis.”
- Symptomatic children suspected of having tuberculosis whose symptoms spontaneously improved in the absence of antituberculosis treatment are included in the “unlikely tuberculosis” classification even if they had initially met other criteria for “unconfirmed tuberculosis.”
- “Unconfirmed tuberculosis” and “unlikely tuberculosis” case definitions should be subdivided to distinguish those with and without immunologic evidence of infection with *M. tuberculosis* (i.e., tuberculin skin test or IGRA positive).
- The limitations of “response to antituberculosis treatment” are noted.
- All children who die following study entry need to be reported, including those who are unclassified due to the timing of the death.

Summary of Changes to Previously Proposed Consensus Case Definitions

Scope remains unchanged

- Remains focused on symptomatic children with clinical suspicion of intrathoracic tuberculosis for evaluation of novel tuberculosis diagnostics in research Entry criteria (unchanged)
- Any current compatible symptom irrespective of duration in a child suspected to have intrathoracic tuberculosis; NOT the same as the clinical features used for clinical diagnosis or disease classification
- Reinforce clear definition of inclusion criteria used for study with careful documentation of presenting symptoms, contact history, and signs
- More clearly articulated in the Figure compared to previous version Intrathoracic tuberculosis diagnostic criteria
- Microbiological confirmation (changed)
- Addition of WHO-endorsed NAAT (e.g. XpertMTB/RIF assay)

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- Clinical signs/symptoms suggestive of tuberculosis (unchanged)
 - Well-defined symptoms/signs that are highly suggestive of tuberculosis
 - Interpretation of chest radiographs (unchanged)
 - Tuberculosis exposure (changed)
 - Time-window reduced to “within the past 12 months.”
 - *Mycobacterium tuberculosis* infection (unchanged) TST and/or IGRA positive; methods and cutoffs used must be specified
 - Response to treatment (unchanged)
 - Clinical case definitions for intrathoracic tuberculosis Confirmed tuberculosis (changed)
 - Positive WHO-endorsed NAAT (e.g., Xpert MTB/RIF) from a respiratory specimen Probable and possible tuberculosis (changed)
 - Consolidated into “unconfirmed tuberculosis” with/without tuberculosis treatment response
 - Differentiate with or without immunological evidence of *M. tuberculosis* infection Unlikely and Not tuberculosis (changed)
 - Consolidated into “unlikely tuberculosis,” irrespective of symptom resolution, treatment received, or alternative diagnosis established

Differentiate with or without immunological evidence of *M. tuberculosis* infection

1. All children in this study will, by definition, already have “known exposure to TB”.
2. Immunological evidence of infection with *M.tb* (i.e. positive TST or IGRA - IGRA in the present study) adds to certainty of infection following known exposure but a negative result does not necessarily exclude infection. Definitions below therefore do not include “immunological evidence of infection” as diagnostic criteria but would be included in reporting of results.
3. Contact screening includes an active case-finding component that will identify children with TB disease at an earlier stage in the disease process than passive case-finding, where children with more severe spectrum of disease are likely to be identified.
4. Some child contacts may have extrapulmonary (extra-thoracic) TB and so there is a need to include these in definitions.
5. There are no data to inform what might constitute an “adequate treatment response” as supportive evidence in this context and so this feature will therefore not be included in the case definition.

The definitions of TB disease that we are using in this trial are taken from the updated international 2015 consensus criteria with consideration of these differences, as follows (please refer to Appendix 7):

Confirmed TB (Bacteriologically confirmed TB)

Defined as positive identification of *M.tb* by culture, Xpert MTB/RIF or MTB/RIF Ultra (Xpert) or another approved PCR-based diagnostic test in a child with clinical or radiological/laboratory evidence of disease. DST will be undertaken in children with positive bacteriology (molecular and/or phenotypic testing). Clinical and radiological characteristics of TB in children are described in tables 1 and 2.

A result will be considered positive if at least one sample of sputum, or other body fluid or

tissue is positive by culture, Xpert or another commercially approved PCR-based diagnostic test. The ERC will also determine the DST of bacteriologically confirmed cases.

Please note that Acid-fast bacilli (AFB)-positive TB alone (that is not positive on culture, Xpert or another PCR-based diagnostic test positive) would not be considered “bacteriologically confirmed”.

Extra-thoracic/extrapulmonary TB will be considered “bacteriologically confirmed” if additional microbiological investigations (e.g. from lymph node fine aspirate, CSF, other clinically relevant samples) have either a positive culture, Xpert/Xpert ULTRA or another approved PCR-based diagnostic test. Positive AFB on histology in isolation would need to be confirmed to be *M.tb*.

Bacteriologically confirmed TB should be classified as pulmonary (intrathoracic), extra-pulmonary (extrathoracic) or both. In principle, the disease features should be reported as completely as possible, to allow for retrospective classification of disease spectrum and severity. All bacteriologically confirmed TB with supportive chest radiograph abnormalities (Table 2) or *M.tb* isolation from a respiratory specimen (sputum, induced sputum, gastric aspirate, nasopharyngeal aspirate, stool, other) will be classified as pulmonary (intra-thoracic) TB.

Unconfirmed TB

Bacteriological confirmation not obtained and at least 2 of the following:

- Symptom's or signs suggestive of TB (as defined)
- Chest radiograph consistent with TB
- Close *M.tb* exposure or immunological evidence of *M.tb* infection
- Positive response to anti-tuberculosis treatment - no time duration specified

Unlikely tuberculosis

Bacteriological confirmation not obtained and criteria for unconfirmed TB” not met

- With *M.tb* infection (*M.tb* test of infection positive)
- Without *M.tb* infection (*M.tb* test of infection positive)

The ERC will reach a conclusion about the diagnosis of unconfirmed TB on the basis of any of the following:

Suggestive clinical findings will include at least one of the following:

- Cough or cervical neck mass ($\geq 2 \times 2 \text{cm}$) for >2 weeks despite a course of antibiotics
- Fever or lethargy for >1 week with or without a course of antibiotics
- Documented failure to thrive i.e. flattening of weight curve crossing centiles, documented weight loss
- Classic gibbus suggestive of spinal TB
- Depressed level of consciousness, new onset seizures or focal neurological signs suggestive of TB meningitis, vomiting without diarrhoea in a child with poor weight gain, or neck stiffness with irritability
- Abdominal lymph nodes on imaging would be considered along with the rest of the clinical picture, as suggestive of abdominal TB.

TB meningitis will be defined using standard international consensus definitions

TB infection

Immunological evidence of infection with *M.tb* (IGRA or TST positive) plus classification as “Not TB.” Please note that TST is not part of the trial schedule of evaluation but may have been completed as part of routine care outside of the trial in child participants.

Indeterminate/unclassifiable TB status

Documented results of the diagnostic evaluation (suspicious symptoms, chest radiograph, laboratory tests) are insufficient for the Endpoint Review Committee (ERC) to reach determination.

Only “confirmed” and “Unconfirmed” TB will be used for primary end point analysis.

Death

Mortality will be classified as death from any cause. TB deaths will be verified using available data (including death certificate, post-mortem, hospital and other clinical information or other as available). Death as a secondary outcome study measure, will consider all -cause mortality as well as death from non-traumatic causes: violent (e.g. homicide) or accidental (e.g. motor vehicle accident) causes. The ERC will review and determine the cause of death, if there are any deaths, in all children participating in the trial.

Details of the death will be obtained from health service medical records, family members or other official indexes (including death certificates). Additional details of the circumstances surrounding the death will be collected to enable the Endpoint Review Committee to evaluate whether the death was likely attributable to TB or the study medication.

Death occurring during a TB episode will be classified as TB death, unless there is clear evidence that the death is unrelated (e.g. motor vehicle accident). A TB death is a death where TB is considered by the ERC to be the most likely/major contributing cause of death. A non-TB death is a death where factors other than TB are considered the most likely/major contributing cause of death. All deaths will be assessed by the ERC.

6.3 PROCEDURES FOR ASSESSING SAFETY

To ensure that the risk to children is minimal in both arms, all children will be comprehensively investigated for TB at screening and any identified prevalent TB cases will be excluded. Children will also be excluded if they have concurrent exposure to both an INH-susceptible and an MDR-TB index case, in order not to withhold treatment proven to be effective for INH-susceptible TB contacts.

Safety assessments at each visit during the 24 weeks of study drug will include symptoms, signs, and laboratory investigations. Safety assessments will also be completed after completion of treatment, through to week 72 as per the schedule of evaluations.

At every study visit (and at unscheduled visits) a symptom checklist will be used to prompt for symptoms of TB disease. While on study drug (or placebo) an additional symptom checklist will explicitly prompt for symptoms relating to possible drug toxicities. The checklist will be part of the CRF completed by the nurse or doctor at each visit. All symptomatic patients will be reviewed by the doctor.

Safety laboratory investigations will be performed at baseline and at week 8. Laboratory investigations will also be performed at unscheduled visits if clinically indicated. Tests will include: haematology (Hb, MCV, WBC, neutrophils, lymphocytes, monocytes, platelets) and biochemistry (ALT, bilirubin). For HIV-positive children, CD4 counts (percentage and absolute) and viral loads will be performed as per **Table 1**.

Cumulative CXR exposure over 48 weeks (1 AP and 2 lateral CXRs) will be within acceptable radiation exposure. Anticipated cumulative radiation dose of CXR is <1 mSV over 48 weeks, which is considerably less than the maximum safe dose and is consistent with international guidelines.

All adverse events will be reported on the case report form. Adverse events (clinical and laboratory) will be graded using the 2017 Division of AIDS toxicity grading scale. Serious adverse events will be defined according to ICH GCP, and will be reported to the MRC CTU according to the agreed timelines (see **Section 7** Safety Reporting).

All TB detected cases (see Section 6.2) will be referred for treatment; linkage to TB care will be verified.

6.4 QUALITATIVE ASSESSMENTS

See **Section 10.1** for details of the Qualitative sub study

6.5 HEALTH ECONOMIC AND IMPACT ASSESSMENTS

See **Section 10.2** for details of the Health Economics sub study.

6.6 DIAGNOSTIC/BIOMARKER/MICROBIOTA ASSESSMENTS

See **Section 10.3** for details of the diagnostic/biomarker and microbiota sub study

6.7 ADHERENCE ASSESSMENTS

Study drug (LFX or placebo) will be dispensed at each clinic visit and will be administered daily by parents/caregivers with treatment adherence support provided. Adherence to TB preventive treatment or placebo (and ART if applicable) will be assessed at clinic appointments and at home visits. Patients will be asked to bring all used drug containers/blister packs. Adherence will be measured from returned pill counts and treatment cards.

6.8 MANAGEMENT OF HIV

Management of HIV will follow national South African guidelines. Routine investigations for

children with HIV, including T-lymphocyte subsets, extended biochemistry panel and viral load testing, will be done using the same blood draw as for additional blood tests in the study, where possible.

Participants living with HIV not on ART at screening will be started on ART immediately and will not be excluded from randomisation. LFX and ART will be started concurrently since there is no evidence indicating potential drug-drug interactions or safety concerns. Children who are already on ART can continue on the same regimen as ARVs have been shown to have minimal interactions with LFX in ongoing studies from South Africa.⁹¹

6.9 MANAGEMENT OF PREGNANCY

All eligible girls of childbearing potential will be followed up with pregnancy tests at their visits if deemed clinically relevant. Any girls who become pregnant on the trial will receive counselling about their options and receive support as required. Pregnant participants will be allowed to discontinue treatment for the duration of their pregnancy but continue follow up only if they choose to. The pregnancy will be followed up to determine the outcome and status of mother and child. All pregnancies should be reported as notable events, unless they meet the safety reporting criteria of a serious adverse event (see Section 7.1.5).

There are no specific safety concerns about the use of the IMP and pregnancy, nor use of oral contraceptives and the efficacy of the IMP.

6.10 EARLY STOPPING OF FOLLOW-UP

If a parent/guardian chooses to discontinue their child from trial treatment, they should always be followed up providing they are willing i.e. they should be encouraged to not leave the trial completely. If they do not wish to remain on trial follow-up, however, their decision must be respected and the patient will be withdrawn from the trial. The MRC CTU should be informed of this in writing as outlined in the MOP.

If the medical data collected during the patient's participation in the trial are kept for research and analysis purposes, they can be anonymised if necessary. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion).

Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

Patients who stop trial follow-up early **will not** be replaced as the total sample size includes an adjustment for losses to follow-up.

Reasons for premature study discontinuation may include:

- Request by the parent/guardian to withdraw.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self.
- At the discretion of the local Ethics Committee, other government agencies as part of their duties, investigator, or industry supporter.

If one or more participating child contacts in a household permanently or prematurely discontinues treatment or study, all other participating contacts within the household will continue to be followed up.

6.11 PATIENT TRANSFERS

If a patient moves from the area, every effort should be made for the patient to be seen at another participating trial site, where feasible. A copy of the patient's CRFs should be provided to the new site and the patient will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the patient; until this has been done, responsibility for the patient lies with the original site.

6.12 LOSS TO FOLLOW-UP

For operational management in the clinic, a patient will be classified as 'lost to follow-up' (i.e. no further efforts to trace the patient are being made) when they have missed 3 consecutive scheduled clinic visits. During this time period attempts should be made to contact the patient via phone (if available) and to follow-up with home visits. Subsequently, if the patient attends clinic and a CRF is received by the MRC CTU, the 'lost to follow-up' status will be reversed.

Extra effort should be made at week 48 to ascertain the status of the patient for primary outcome assessment.

6.13 ASSESSMENTS AT TRIAL CLOSURE

The trial will be considered closed after the last patient has attended their week 72 visit and all data entered and queries have been resolved (see **Section 11.4** Trial Closure).

7 SAFETY REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 7.1** lists definitions, **Section**

7.3 gives details of the investigator responsibilities and **Section 7.4** provides information on MRC CTU responsibilities.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial protocol. These definitions are given in **Table 3**.

Table 3. Adverse Event Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.
Hospitalisations for a

pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision). This therefore includes LFX and placebo.

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

7.1.2 ADVERSE EVENTS

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse events will be graded according to DAIDS criteria and published criteria for joint, muscle and bone complications.⁸¹ Grade 3, 4 or 5 (death) adverse events will be documented on specific Case Report Forms (CRFs). Serious adverse event reports will be submitted to the MRC CTU within one working day of the event being reported, and again at the resolution of the management of those events. Management of adverse events will be described in detail in the Manual of Operations (MOP) and appropriate management for these events will be initiated at a local level, managed by the NTP and/or other government (public) clinics or hospitals as appropriate.

Adverse events will be monitored carefully throughout treatment by research staff. Child participants will be reviewed at baseline, then every 4 weeks while taking treatment. At each visit, participants will be assessed clinically and at weeks 8 and 24 will have blood tests to check for liver toxicity (see **Table 1**). Additional clinical review and diagnostic tests will be provided free of charge if other complications are identified.

Parents/caregivers will be told about adverse events, and will be able to receive free clinical assessment if any concerning symptoms develop.

7.1.3 EXEMPTED ADVERSE EVENTS

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

7.1.4 DISEASE-RELATED EVENTS

All adverse events meeting the definitions above should be reported on study CRFs, regardless of their relationship to TB. In particular, all deaths should be reported as fatal SAEs.

7.1.5 PREGNANCY AS A NOTABLE EVENT

Pregnancy whilst on the trial should always be reported as a notable event within the same timelines as an SAE. Pregnancies do not constitute SAEs unless they result in a condition that meets the seriousness criteria defining SAEs. The clinical team responsible will be informed of the mother's participation in the trial and will be asked to inform MRC CTU at UCL if there is any suspicion of any adverse effect of the trial medication. Adverse events occurring in an infant born to female trial participants within 28 days of delivery should be reported in order to evaluate for a possible adverse reaction related to *in utero* exposure to the study drugs. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study should also be reported as an SAE. Any event fulfilling the criteria of an SAE (e.g. congenital abnormality or birth defect) should be reported within 1 working day of the site becoming aware of the event. Follow-up of a child born to the partner of a male participant (who was taking trial treatment at the time of conception) will be according to local practice. At the end of pregnancy, the investigator will complete a Pregnancy Outcome Case Report Form.

7.1.6 TOXICITY

The following medications may potentially have interactions with LFX and should be carefully monitored. These drugs are not necessarily contra-indicated.

- Antacids, multivitamin, or other medicines or supplements that have magnesium, aluminum, iron, or zinc
- Sucralfate
- Didanosine
- NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief contain NSAIDs. Taking an NSAID while taking LFX may increase the risk of central nervous system effects and seizures.

These drugs should ideally not be administered within 4 hours of ingesting LFX

Additional drug interactions, with drugs rarely used in children, may include:

- Blood thinners (warfarin, coumadin)

-
- Oral anti-diabetes medicines or insulin

In general, potential drug toxicity will be evaluated as described in the schedule of evaluations.

If study drug is held for toxicity, participants will have 28 weeks from enrolment to complete the 24 weeks of treatment.

Grades 1 and 2 toxicity: Participants may continue study drug, at the discretion of the site investigator, with careful follow-up. However, there will be a low threshold to discontinue study treatment at the first sign of tendon pain or tendon inflammation.

The risk/benefit of LFX preventive therapy should be considered by the clinical team in the context of a healthy child with MDR-TB exposure and high risk of TB disease progression. Grades 3 and 4: Study drugs should be held until: a) return to baseline (entry visit levels) if baseline was > Grade 2, or b) until $\leq$ Grade 2 if baseline was $\leq$ Grade 2. Study drug may be permanently discontinued at the discretion of site investigator.

Management of specific adverse events felt to be due to study drug is addressed in **Appendix 8**.

Reporting

The following incidents will be systematically reported:

- Breaches of confidentiality following a TB or HIV diagnosis
- Needle stick injuries
- Grade 3 and Grade 4 adverse events
- All deaths (due to any cause) during follow-up of child contact
- All Grade 1 and 2 adverse events will be systematically collected

7.2 OTHER NOTABLE EVENTS

- TB end points should be captured on the appropriate CRFs and should be reported within one working day as a notable event. Please also refer to the MOP.

7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes, the toxicity (symptoms) section of the follow-up CRF and the adverse event log, and sent to the MRC CTU and ethics committees within **the agreed** time scale as outlined in the TB-CHAMP MOP. SAEs should be notified to the MRC CTU within one working day of the investigator becoming aware of the event and reported to local ethics committees as required.

7.4 INVESTIGATOR ASSESSMENT

7.4.1 SERIOUSNESS

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definition given in **Table 3**. If the event

is serious then an SAE Form must be completed and the MRC CTU notified within one working day of the investigator becoming aware of the event. All SAEs require reporting, including those related to TB disease.

7.4.2 Severity or grading of adverse events

The severity of all AEs and/or ARs (serious and non-serious) in this trial is consistent with international norms, will use the revised Division of AIDS (DAIDS) adverse grading for the adverse events (DAIDS 2017). [<https://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>]. These tables should be specifically consulted and followed for assessments and grading of both clinical and laboratory abnormalities.

7.4.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in **Table 4**. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 4. Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to **Section 5.2.4**.

7.4.4 Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the investigator must make an initial assessment of the expectedness of the event but the Sponsor is responsible for making the final assessment.

The reference safety information (RSI) for the IMP used in the TB-CHAMP trial is contained within Section 4.8 of the relevant Summaries of Product Characteristics (SmPCs). The RSI is used to assess the expectedness of events reported on SAE CRFs.

The correct and approved versions of the SmPCs will be available online via the WHO web page (<https://extranet.who.int/prequal/WHOPAR/tb277>). The CTU will inform investigators if there is a change to the RSI.

An unexpected adverse reaction is one not previously listed in the Reference Standard Safety Information (RSI) or one that is more frequent or more severe than previously reported. The RSI for the IMPs used in the CHAMP trial is contained in the relevant Summaries of Product Characteristics (SmPCs). The RSI is used to assess the expectedness of events reported on SAE CRFs. The correct and approved versions of the SmPCs are available online via the web page (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021721s020_020635s57_02_0634s52_lbl.pdf). The CTU will inform investigators if there is a change to the RSI. The definition of an unexpected adverse reaction (UAR) is given in **Table 3**. Please see **Appendix 8** for a list of expected toxicities associated with the LVX, the drug being used in this trial. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.4.5 Notification

The MRC CTU should be notified of all SAEs within one working day of the investigator becoming aware of the event.

Investigators should notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU until trial closure.

7.4.6 Notification Procedure

1. The Event Form must be completed by the investigator (the consultant named on the Signature List and Delegation of Responsibilities Log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and faxed or emailed as appropriate. The responsible investigator should subsequently check the Event Form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting, the event, and why it is considered serious.

The Event Form must be emailed securely to the MRC CTU tbchamp.mrcctu@ucl.ac.uk

Follow-up: patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further Event Form,

indicated as 'Follow-up' should be completed and faxed to the MRC CTU as information becomes available. Extra annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, month of birth and initials only. The patient's name should not be used on any correspondence and should be deleted from any test results.

Staff should also follow their institution's procedure for local notification requirements.

SAE REPORTING

Within one working day of becoming aware of an SAE, please securely email a completed Event form to the MRC CTU: **tbchamp.mrcctu@ucl.ac.uk**

7.5 MRC CTU RESPONSIBILITIES

Medically qualified staff will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The Trial sponsor, Stellenbosch University, is responsible for the onward reporting of SAEs, SUSARs and other SARs to the South African regulatory authority, SAHPRA, and the relevant research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the MRC CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

The Sponsor will submit Annual Safety Reports in the required format to Competent Authorities (Regulatory Authority, i.e. SAHPRA – monthly, and Ethics Committees - annually).

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the Research Governance Committee (RGC) and has led to the development of quality management documents.

8.2 CENTRAL MONITORING AT MRC CTU

Each site will be responsible for its own data entry and local trial management. Data will be dually entered into the trial database directly at the site. The site will retain the original CRF. Data stored on the central database will be checked by personnel authorised by the MRC CTU for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the site will be contacted and asked to verify or correct the entry. Changes will be made on the original CRF and entered into the database at the site. MRC CTU will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

Other essential trial issues, events and outputs will be detailed in the monitoring and quality management documents that are based on the trial-specific Risk Assessment.

8.3 ON-SITE MONITORING

Locally appointed staff or staff from MRC CTU will visit clinical sites to validate and monitor data and an independent local monitor will be employed to make regular visits to the trial sites. The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the monitoring and quality management documents. The monitoring plan will also detail the procedures for review and sign-off.

A detailed site initiation visit with training will be performed at each study site by staff from Stellenbosch University and CTU who will be specifically trained for this role. The site initiation visits will include training in the administration and side effects of study drugs, as well as the trial procedures.

Monitoring and site training will be carried out at least twice a year at each site by MRC CTU staff or locally based monitors. The monitoring will adhere to the principles of ICH GCP and will follow an agreed monitoring plan.

Monitors will:

- verify completeness of ISF
- confirm adherence to protocol
- review eligibility verification and consent procedures
- assess missed clinical event reporting
- verify completeness, consistency and accuracy of data being entered on CRFs
- evaluate drug accountability
- provide additional training as needed

The monitors will require access to all participant medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved in a reasonable time frame.

8.3.1 Direct Access to Patient Records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to index data and documents as required. Participants' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from index documents:

- all signed consent forms
- dates of visits including dates specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- all clinical endpoints
- all serious/severe adverse events
- routine patient clinical and laboratory data
- drug compliance
- dates drug dispensed and (if necessary) drugs returned
- pharmacy/clinic drug logs
- concomitant medication

8.3.2 Confidentiality

The investigator must assure that participants' anonymity will be maintained and that their identities are protected from unauthorized parties. Participants will be assigned a trial identification number and this will be used on CRFs; participants will not be identified by their name. The investigator will keep securely a patient trial register showing identification numbers, names and date of birth. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality. All records will be kept in locked locations. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

The household randomisation list will be centrally generated by the MRC CTU using block randomisation, with varying block size and allocation in a 1:1 ratio to the 2 arms. Randomisation will be stratified by centre.

All child/adolescent contacts within a household will be allocated to the same study arm. Since numbers of clusters are large relative to household size, the design (cluster) effect is likely to be small.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY EFFICACY OUTCOME

The primary efficacy outcome measure is TB disease (including TB death) by 48 weeks post randomisation. See **Section 6.2** for definitions of TB.

All potential TB outcomes and all causes of death will be adjudicated by an independent ERC blinded to treatment allocation, based on available clinical, DST, microbiological and molecular data using standard case definitions (see Appendix 7).

The primary analysis will include confirmed and unconfirmed TB only, including TB deaths.

9.2.2 SECONDARY EFFICACY OUTCOMES

Secondary efficacy outcomes are

- TB disease or death due to non-traumatic causes by 48 and 72 weeks
- TB disease by 72 weeks
- Death due to non-traumatic causes by 48 and 72 weeks
- Death due to any cause by 48 and 72 weeks

9.2.3 SAFETY OUTCOMES

The primary safety outcome is adverse events grade ≥ 3 that are at least possibly associated with study drug during 24 weeks of treatment. Adverse event grade ≥ 3 is a secondary safety outcome.

9.2.4 OTHER SECONDARY OUTCOMES

- Proportion of LFX or LFX-placebo doses taken by 24-28 weeks
- Incidence of LFX resistance in children/adolescents from either arm developing culture-confirmed TB.

9.2.5 ADHERENCE

Adherence will be measured by the amount of drug taken as reported, from the total expected. This will be expressed as the proportion of allocated doses taken by 24-28 weeks of treatment duration. The threshold defined for adequate treatment adherence is 80% (see **Section 5.1**). Treatment adherence will be summarised for each treatment group using descriptive statistics and compared using appropriate significance tests.

9.3 SAMPLE SIZE

While the randomisation will be performed at the household level, because of heterogeneity and some level of uncertainty as to the household size and the desire to be more conservative with respect to ensuring that the study is adequately powered, the target enrolment will be based on the total number of child/adolescent HHCs enrolled.

For sample size determination, we have assumed a 60% reduction in TB disease incidence by 48 weeks (i.e. 60% efficacy of LFX), from 7% in the control arm to 2.8% in LFX arm, at a 5% two-sided significance level.

The assumed 7% primary outcome rate in the control arm is based on the expected distribution of child/adolescent HHCs who meet the inclusion criteria, and conservative assumptions on the rates of the primary outcome in each risk category. Local observational epidemiological studies from South African sites have supported these assumptions.

An intra-class correlation (ICC) within a household is conservatively assumed to be 0.10 based on previous data from large household contact study in 1200 children in Cape Town (personal communication, Hesselning).

Allowing 10% loss to follow-up and assuming two HHCs per household and the above assumptions, we will require a total of 1009 HHCs (505 HHCs per arm), from an estimated 505 households to achieve 80% power (see **Table 5**). All sample size assumptions will be reviewed at interim analysis.

Change in study inclusion criteria from version 3.0 protocol: considerations for power calculations

The target sample size remains the same following the change in inclusion criteria to include children/adolescents aged 5-17 years old with evidence of TB infection or living with HIV, for the following reasons: We expect the overall mean number of child and adolescent HHCs enrolled per household to be approximately 2.0, consistent with the original assumption. This is because the observed mean up to 1 October 2020 is 1.8, and is expected to increase to 2.5 for enrolments from version 3.0 onwards (corresponding to 30% of all households in the overall study). The overall TB event rate in the control arm is expected to increase slightly with the change in inclusion criteria assuming: (i) 40% of children/adolescents aged 5-17 years are IGRA-positive (ii) the effects of age and IGRA status on risk of TB are consistent with the findings by Martinez *et al.*⁸⁷ (ii) LFX efficacy remains 60% among older children/adolescents with evidence of TB infection or living with HIV.⁸⁷

Table 5: Total number of children/adolescents required*, for varying control arm event rate and LFX efficacy

LFX efficacy	% TB cases by 48 weeks in control arm		
	8%	7%	6%
50%	1352	1556	1832
60%	876	1009	1187
70%	601	694	814

*To achieve 80% power for the study, assuming 2 child/adolescent contacts per household, 10% loss to follow- up and 5% two-sided significance level test.

9.4 INTERIM MONITORING & ANALYSES

The Independent Data Monitoring Committee (IDMC) will review study conduct and safety data regularly, and could in exceptional circumstances recommend termination of the study. An IDMC Charter will be drawn up that describes the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (with a description of any stopping rules and/or guidelines). Safety, including assessment of arthropathy/arthritis and liver toxicity, will also be reviewed by the IDMC. The IDMC will be asked to advise on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further participants.

There will be one planned interim efficacy analysis, which will take place after at least 500 household contacts have been enrolled and followed up for at least 24 weeks.

The IDMC will advise the TSC whether the trial should be stopped if in their view the randomised comparison has provided proof beyond reasonable doubt that the trial intervention is clearly indicated or clearly contra-indicated in terms of a net difference in efficacy or adverse events or, there is proof beyond reasonable doubt from other studies to influence clinic staff in their management of participants that is incompatible with continuing. Such proof would normally require a difference in event rates between the two study arms in the trial to be significant at $\alpha < 0.001$.

9.5 ANALYSIS PLAN

The analyses will be described in detail in a full Statistical Analysis Plan (SAP), which will be finalised prior to data analysis. This section summarises the main issues only.

While randomisation will be at the household level, inference will be at the individual level since the objective is to reduce the percentage of children experiencing the primary outcome.

The primary analysis will include all randomised participants, apart from any subsequently found to have had TB in the first 30 days following enrolment, i.e. based on modified intention-to-treat (mITT) approach.

An intention-to-treat (ITT) analysis including all randomised participants will also be performed. The incidence of TB will be compared between arms using survival analysis methods. Kaplan-Meier estimates of the cumulative proportion of participants with the primary outcome by weeks 48 will be presented. For the final primary analysis, generalised linear mixed models will be used, allowing for intra-household correlation. The effect of LFX will be assessed based on data from all participants, stratified by age group (<5 years versus 5-17 years). Heterogeneity of the treatment effect over age group will be checked by assessing for interaction, with the overall treatment effect presented if there is no evidence of interaction. Regression models will be adjusted for centre (stratification factor at randomisation), and for any clinically important imbalances in baseline characteristics observed between arms.

Additional secondary and sensitivity analyses will be performed to confirm the primary finding and will be detailed in the full analysis plan.

Efficacy of LFX will be expressed as 1 minus the relative risk (RR) for LFX when compared to placebo.

10 ANCILLARY STUDIES

10.1 QUALITATIVE RESEARCH

In South Africa, the epidemiology of TB is closely related to circumstances of social privation, particularly: (a) over-crowded living conditions, (b) inadequate health service support – due to accessibility, care standards, and patient behaviour, (c) comorbidity with ‘diseases of lifestyle’ – such as substance abuse, and (d) marginalization due to TB-related and other intersecting stigmas.

Similarly, MDR-TB disproportionately affects the socially marginalized and vulnerable, particularly young children. Understanding how specific social processes facilitate TB transmission, late presentation for care, and poor adherence outcomes is important for each stage of the development, implementation, evaluation, and roll-out of novel treatment, prevention regimens and care models. Further, effectively delivering treatment and prevention is largely dependent on the vagaries of local social processes in the health system. Healthcare workers face disproportionate risk of TB themselves, can perpetuate TB-related stigma, and are core arbiters of TB-related information.

The social science components of TB-CHAMP therefore aim to:

1. Describe TB-related health stakeholders’ perceptions about the current TB care and prevention environment and their views on the proposed MDR-TB prevention trial intervention in children,
2. Document in detail how the intervention is implemented on the local level
3. Characterise patients’ (and their families’) experiences of the TB-CHAMP intervention specifically, and the TB prevention, treatment, and care continuum specifically.

The social science work will be carried out by a dedicated team of social scientists and researchers as described below, based on the availability of additional funding.

Design

There are three distinct data collection components to the social science:

1. Part A – Key informant interviews (n=approximately 20) with stakeholders (in health services and at community level) about their pre-trial implementation perceptions about the intervention and its delivery to inform engagement and training activities. This will be implemented before the start of the trial to inform study implementation, as part of feasibility work.
2. Part B – Mixed-methods (including interviews, group discussions, structured observations and documentary review) describing how the trial is *actually* implemented to inform policy-level interpretation of the trial results from the perspective of implementation (e.g. if the trial outcome warrants scale-up, then these data will inform operational-level roll-out planning). Documentary data (such as minutes of stakeholder meetings) are collected throughout the trial period. Interviews, group discussions and structured observations are collected in annual rounds starting in parallel to recruitment for the trial and lasting approximately 40

weeks of data collection, 24 weeks of data processing, and 12 weeks report writing and refining for the subsequent round.

3. Part C – A qualitative cohort (n=approximately 20 patients) recruited at the start of the trial and followed at week intervals throughout the intervention implementation period as per the trial schedule of evaluation. Participatory, qualitative data about patients' and their families' /caregivers' experiences of the intervention, and MDR-TB prevention and treatment generally, (including relevant contextual data) will be collected by ethnographic case-study design. Cases will be purposively sampled for maximum variability and selected for follow-up in consultation with the senior social scientist and study leadership.

Likely outcomes

Generally, the social science contributes two cross-cutting analytic themes:

1. Acceptability, suitability and satisfactoriness of the intervention (and each intervention implementation element, e.g. household contact tracing of children exposed to MDR-TB, TB screening, medication administration, etc.) from both a health systems and patient/family perspective
2. Transferability of trial outcomes to other contexts

Specifically, the social science component of TB-CHAMP will lead to:

1. A short working report on stakeholder's perspectives about the intervention (based on rapid analyses) delivered to the study team before intervention implementation and used for planning purposes.
2. Academic papers describing health system readiness for each intervention implementation element by the end of the first year of the trial, and comparison of sites.
3. An academic paper describing patient perspectives on the novel preventive strategy by the end of the trial.
4. Contributions to the trial conclusion report as determined by study outcomes.
5. Potentially, other academic contributions throughout the study period as determined by the data collected.
6. Opportunities for PhD and/or Masters level training

10.2 HEALTH ECONOMICS STUDIES

This sub-study will investigate the costing and cost-effectiveness of the trial interventions for both families and healthcare systems at the collaborating sites. This will involve collecting costing data from each of these sites, including costs associated with the interventions as well as costs associated with children developing MDR-TB disease. Since all 4 sites are South African, standard costing data (e.g. lab testing through the National Health Laboratory services; NHLS) will be used. We will prospectively measure all costs related to LFX delivery using a micro-costing approach. Component costs will include overheads, labour, equipment, drugs and other consumables, transportation, hospitalisation and miscellaneous costs. Data will be collected from each site in a standardised way using national cost databases as data collected by local site investigators. We will assess patient/caregiver costs using validated tools and healthcare costs through budgetary analysis, time-motion studies, employee and key informant interviews, and prospective logbooks.

Using decision analysis with Markov modelling, we will project clinical and economic outcomes in disability-adjusted life years (DALYs) averted, and the ICER as the incremental cost per incremental DALY averted. The primary outcome will be the ICER, comparing LFX against placebo among child MDR-TB contacts, from the societal perspective over a lifetime analytic horizon. Health outcomes will be calculated from the societal perspective over a lifetime analytic horizon and we will determine quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) and life years gained (LYGs). This will be based upon EQ-5D (health-related quality of life) data and through applying morbidity-weights to MDR-TB and MDR-TB-free survival. The cost savings from adopting this strategy at the national level will then be estimated based upon national estimates of childhood MDR-TB incidence in South Africa. The analyses will be probabilistic. A number of subgroup and scenario analyses will be undertaken, including based upon the HIV status of children, study site and by costing alternative drug combinations, especially delamanid.

We will conduct one-way sensitivity analyses on all model parameters, multi-way sensitivity analyses on parameters most critical to the cost-effectiveness estimate, and a probabilistic uncertainty analysis where all parameters are varied simultaneously over distributions to construct 95% uncertainty ranges and cost-effectiveness acceptability curves.

We will include secondary analysis from the healthcare perspective, using cases averted as outcome measure, and scenario analyses designed to inform generalisability.

10.3 DIAGNOSTIC AND BIOMARKER SUB STUDIES

Within the framework of the trial there is enormous potential to explore other scientific questions. These include understanding the biology and pathophysiology of *M.tb* in children as well as improving our understanding of why some children develop TB following exposure and infection. In addition, the ability to diagnose both TB infection and disease in children are evolving fields and we aim to explore novel techniques in this area. Finally, we will explore the impact of LFX on the host, to determine if it has any benefits or risks beyond its effect on *M.tb*.

Below, we outline study questions that we propose to carry out within the framework of the trial. Although we will collect relevant samples for these studies and ask for consent from families to participate at recruitment to the trial, the funding of these studies and the details of how they will be carried out will be documented in further applications.

TB disease diagnostics

For children at baseline or under follow up who develop symptoms of TB disease, we plan to evaluate different novel culture molecular techniques (including the new XpertMTB/RIF Ultra). We will also evaluate a recently-described blood RNA expression signature⁸² and other novel biomarker as diagnostic tests for TB infection and disease. In addition to using the RNA expression as a diagnostic test, we plan to use the results from these samples to identify differences in up- and down-regulated immunological pathways between children infected but well and those who progress to disease.

TB infection diagnostics

The current measures of TB infection (TST and IGRA – with IGRA being used in this trial) have limited sensitivity and specificity in young children and in children with HIV. We will evaluate whether any baseline blood RNA expression signature correlates better with a validated exposure score than the traditional infection tests.

Predictive biomarkers

If it were possible to determine which children with TB infection were more likely to progress to TB disease, not only would this shed light on the underlying immunological processes involved in containing the mycobacteria, but would also permit more efficient targeting of infection treatment. We plan to evaluate whether any baseline blood RNA expression signature correlates with subsequent progression to disease. The ratio of monocytes to lymphocytes in the blood has long been used to determine activity in patients with TB and recently, in infants living with HIV in South Africa, the ratio has been shown to correlate with risk of development of TB.⁸³ We plan to evaluate if this ratio is associated with incident TB disease in children following exposure to TB within our trial.

We will also evaluate whether any characteristics of the host gut microbiome predispose to subsequent disease progression.

Triggers for disease progression

Complex relationships exist between viral infections and susceptibility to bacterial infections. Examples include, an increased susceptibility to pneumococcus post influenza infection, increased susceptibility to Group A *Streptococcus* infections post varicella infection and susceptibility to multiple bacterial pathogens post measles infection. There is emerging evidence that individuals are at increased risk of TB following influenza infection.⁸⁴ We plan to investigate, in a child who is infected with *M.tuberculosis* but is containing the organism, whether incident viral infection disrupts this equilibrium and leads to the progression to TB disease. To this end we will collect regular serum samples from children to test for respiratory viruses and determine if there is a temporal relationship with the development of TB disease as per the schedule of evaluations (see under serum sample collection).

Impact of LFX

One of the secondary outcomes of the trial is to determine if children who are given LFX and do develop TB disease have higher rates of *M.tuberculosis* that are resistant to the fluoroquinolones as compared to placebo. In addition, we seek to evaluate some of the other effects of LFX. INH is an effective antibiotic against *M.tuberculosis* but has limited activity against other bacteria. LFX, alternatively, has activity against aerobic gram-positive and gram-negative organisms, some activity against anaerobic bacteria and good activity against atypical bacteria. We will evaluate whether six months of LFX influences the stool or respiratory microbiome and also whether this treatment leads to the development of fluoroquinolone resistance in non-mycobacterial bacteria, such as pneumococcus. We will do this by collecting stool and respiratory samples at baseline in all children and then at follow up.

Finally, there is emerging evidence that co-trimoxazole, a broad-spectrum antibiotic, has non-specific beneficial effects on children living with HIV, such as reduced anaemia and

better growth.⁸⁵ It is now being evaluated as a therapeutic intervention in malnourished children without HIV in developing countries. We will evaluate the non-specific effects of the broad-spectrum antibiotic LFX within this trial, including growth and anaemia.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki (2013). It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP).

11.1.2 CENTRE/SITE COMPLIANCE

The centre will comply with the principles of GCP and applicable national regulations. An agreement will be in place between the centre and DTTC, Stellenbosch University, setting out respective roles and responsibilities.

The centre/site will inform the CTU as soon as they are aware of a possible serious breach of compliance, so that the CTU, in consultation with DTTC, can report this breach to the trial sponsor with onward reporting to Ethics and Regulatory bodies as necessary. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial

11.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 5 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities and the Sponsor with suitable notice.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

The choice of regimen, including a single drug, LFX, compared to placebo, in MDR-TB exposed children and adolescents, is well-justified and presents equipoise, given the lack of any evidence from clinical trials to date (in adults or children) on management of MDR-TB exposed individuals. WHO specifically does not recommend any specific drug regimen in household contacts of infectious MDR-TB cases and has again reiterated this statement in 2018, calling for the conduct of placebo-controlled trials. It must be emphasized that the default standard of care for MDR-TB contacts in most of South Africa is currently no investigation (and no drug regimen). The study team has consulted with experts in the field of bio-ethics both in South Africa and internationally (see letter of support).

In order to ensure the minimum of risk to participants in both arms, all children and symptomatic adults in the household will be comprehensively screened for TB disease at baseline; any cases detected will not be eligible. Children/adolescents will also be excluded if they have exposure to both a drug-susceptible and MDR index case, as it would not be ethical to

withhold treatment that is proven to be efficacious for drug-susceptible TB contacts. Children/adolescents with known INH susceptible exposure will be excluded and referred for INH preventive therapy. Children with confirmed RIF mono-resistant exposure will also be excluded if identified, and referred for INH preventive therapy. All participants will be closely followed so that if disease develops, it is detected early and treated effectively. Disease detected in contacts in this active surveillance study is also likely to be non-severe, since there would be limited diagnostic delay, based on experience from large South African contact investigation studies in children. Children/adolescents with non-severe MDR-TB would typically require less aggressive MDR-TB treatment. All children and all adults who have symptoms suggestive of TB will be referred for TB investigation and care by the research team. The research sites are all closely linked to the local TB programs, clinics and hospitals. All participants will be followed for 18 months.

Participants developing any adverse events will be investigated and managed aggressively; arthralgia and diarrhoea will be closely monitored, along with other potential adverse effects.

Total blood volumes and volumes required per study visit are minimal and considerably less than the allowed blood volumes allowed for research in children in South Africa and internationally. We will be taking a maximum of 32-34 ml in participants over the total study period, regardless of HIV status. Testing for TB is standard of care and generally well tolerated and safe (gastric aspirates or sputum induction).

Cumulative CXR exposure over 48 weeks (3 AP and 3 lateral CXRs) will be within acceptable radiation exposure. Anticipated cumulative radiation dose of CXR is <1 mSV over 48 weeks, which is considerably less than the maximum safe dose and is consistent with international guidelines. CXR are also routinely undertaken in children with MDR-TB exposure in routine clinical settings in South Africa.

In summary, this trial is considered to pose substantial benefit to clinical care and guidelines in South Africa and international settings, while posing minimal risk to child and adolescent study participants and their families. Risk will be assessed on an ongoing basis, and will be part of formal interim analysis.

A parallel but independent large MDR-TB prevention trial planned for implementation in Viet Nam, the V-QUIN study (PI: Greg Fox), is planning on using the identical drug regimen (LFX vs. placebo) in adult and child household MDR-TB contacts, as in our proposed study. The TB-CHAMP and V-QUIN trial teams have undertaken to harmonise and standardise clinical data collection, end point definitions and, following both studies' protocol-defined analyses, combine data in future to better inform global guideline development and the care of high-risk MDR-TB household contacts in different settings in future. The same approach would be followed with other planned MDR-TB prevention trials. Early dissemination of TB-CHAMP trial data, as relevant, as is planned, may also inform the design and implementation of other future planned MDR-TB prevention trials.

11.2.2 ETHICAL APPROVALS

Before initiation of the trial at each site, the protocol, all informed consent forms, and information materials to be given to the prospective patients and carers will be submitted to each ethics committee for approval, according to national guidelines including local ethics committees, local government (e.g. NTP), and the South African Health Products Regulatory Authority (SAHPRA). Any further amendments will be submitted and approved by each ethics committee.

The rights of the child/adolescent and/or their carer to refuse to participate in the trial without giving a reason must be respected. After the child/adolescent has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the child. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

The participants and/or their carers will be informed fully of known risks and possible benefits by means of a patient information sheet and this will be reinforced by discussions with the trial research teams at the individual sites prior to enrolment.

Patients' confidentiality will be maintained throughout the trial. Data submitted to CTU and samples sent to the central testing facility will be identified only by the trial number and patient initials.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted to the national competent or equivalent authority, as appropriate in the country where the trial will be run.

The progress of the trial and safety issues will be reported to the regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 TRIAL CLOSURE

The trial will close after the last randomised participant have been followed up for 72 weeks, all the data captured in the database, all queries resolved, and the database is locked.

12 INDEMNITY

The sponsor of the trial is the Stellenbosch University. Stellenbosch University therefore accepts overall responsibility for this trial. Clinical trial insurance has been obtained by the sponsor for all trial participants at all trial sites.

13 FINANCE

The trial is supported by grant funding from UNITAID, the Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the Wellcome Trust and the Medical Research Council (MRC UK), and the South African Medical Research Council (SAMRC), awarded to Stellenbosch University.

The trial will be coordinated by the MRC CTU at UCL. A written agreement with the Sponsor and UCL (on behalf of MRC CTU) will outline the roles, responsibilities and finances of these delegated coordination duties. A written agreement will also be made between the Sponsor Site Principal Investigator and participating sites/centres.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

14.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the protocol and site principal Investigators, other lead investigators (clinical and non-clinical) and members of the MRC CTU trial team. The TMG will be responsible for the day-to-day running and management of the trial. It will meet approximately three times a year at least one of which will be in-person. The full details can be found in the TMG Charter.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the trial statisticians. The IDMC will meet within 6 months of the trial opening; the frequency of meetings will be dictated in the IDMC charter. The IDMC will consider data using the statistical analysis plan (see **Section 9.5**) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial.

Further details of IDMC functioning and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

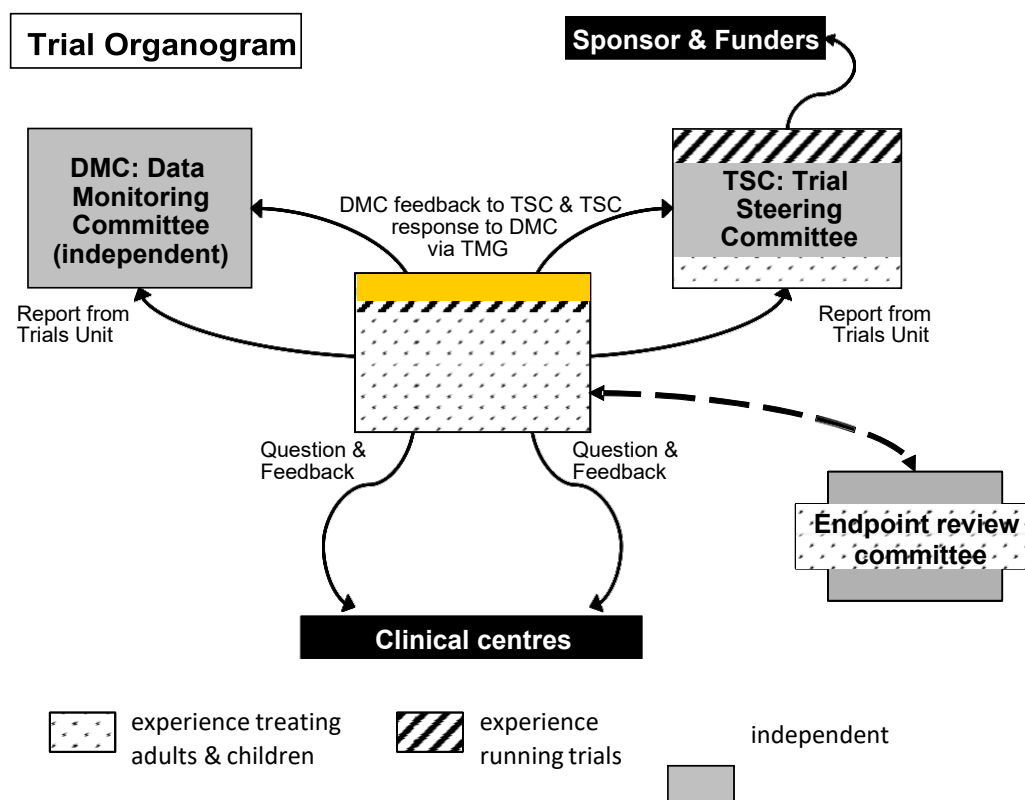
14.4 ENDPOINT REVIEW COMMITTEE (ERC)

The central blinded Endpoint Review Committee (ERC) will have the following functions:

1. To determine the primary end point status for all patients suspected of developing TB during follow-up.
2. To examine all evidence and adjudicate cause of death based on all available indexes of data, blinded to trial arm

Please refer to separate ERC charter.

Figure 4. Trial Organogram



14.5 ROLE OF STUDY SPONSOR

Stellenbosch University is the Sponsor of TB-CHAMP and delegates part of this responsibility to the MRC CTU at UCL to oversee the implementation of the study by ensuring that arrangements are put into place for adequate management, monitoring, analysis and reporting of the trial.

15 PUBLICATIONS

The TB-CHAMP TSC is the custodian of the data and specimens generated from the TB-CHAMP trial; TB-CHAMP trial data are not the property of individual participating investigators or health care facilities where the data were generated.

It is anticipated that a number of opportunities will arise for publication during the course of and following completion of the TB-CHAMP trial. This will include publication papers (including abstracts) for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the Lancet and from the publication policies used in MRC CTU trials.

All manuscripts are to be approved by the TMG and TSC before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the IDMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial or associated substudies will be conducted or presented before the end of the trial, other than those for interim review by the IDMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

In line with UK MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event. All publications will acknowledge the trial's funding indexes.

For all publications, the TMG will nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have made a substantive academic or project management contribution to the work that is being presented. "Substantive" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will

be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC (and the IDMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the IDMC before the end of the trial), they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC (and the IDMC before the end of the trial). Any requests for access to data will be considered as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team.

In general, there will be a strong emphasis on supporting postgraduate students and on capacity building, especially at local site level, in South Africa.

Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The IDMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

16 PROTOCOL AMENDMENTS

Changes to protocol version 1.0 creating version 2.0, dated 13 May 2019

1. Title page – ISRCTN number was added
2. Page iii - Sponsor section: updated to state that queries relating to sponsorship should be addressed to the PI at Stellenbosch and not the MRC CTU at UCL.
3. Page iii – Funding section – clarified that funding from SA MRC is through SHIP programme. Spelling of Macleods was corrected
4. Page iv – ISRCTN number was added under Trial Registration
5. Page iv - the contact details for SAE reporting updated
6. Pages iv – x – TB-CHAMP staff list updated
7. Page xi –Safety Outcomes and Secondary Outcome Measure(s) updated, sample size and duration of trial was reduced. A detailed statistical review was completed by the trial statistician, Dr. Angela Crook, and the TSC independent statistician, Professor Carl Lombard, SA MRC. In summary, our revised sample size estimate is n=1009, assuming a 60% levofloxacin efficacy. This would imply that we could complete enrolment by February 2021 and complete follow-up by August 2022. We are currently observing the expected primary end point TB event rate in our trial
8. Page xiii – Trial Schema was updated to reflect reduced duration of trial and for clarification purposes
9. Page xiv – Schedule of Evaluations - The following changes were made:
 - IGRA will be done on all participants at the week 24 visit to assess conversion and revisions in children on levofloxacin vs. placebo
 - Routine chest X-rays at week 12 have been removed. All symptomatic children will be investigated as per protocol guidelines.
 - Follow-up has been decreased to 72 weeks. >90% of all TB exposed children that develop TB disease, do so within the 12 months following exposure and infection. We are following children for 18 months, which is adequate to capture TB events and makes the trial more feasible.
 - EQ-5DY to be implemented at weeks 12, 24 and week 72.
 - Acceptability questionnaire has been omitted at weeks 12 and 16 to avoid unnecessary data collection.
 - WHO staging blood volume was removed (no blood needs to be drawn to stage a child)
 - CD4 count and viral load will be done at week 72 (final visit).
 - Bacteriological investigation, DST and genotyping in adult index case have been omitted. These results would only be useful where child participants develop TB, for comparative purposes and to confirm the source of infection. By the time index cases are recruited they are on treatment and often bacterial investigations are negative. In many instances study team will have access to index case sampling done in routine care.

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- TB register surveillance was omitted since this would add limited additional information
 - The following investigations for the sub studies have been removed from the list of procedures:
 - Nasopharyngeal swab for DTTC site for bacterial/viral studies, microbiome.
 - Urine biomarker for DTTC site.
 - Routine safety bloods will not be done at Week 16 visit. All symptomatic children will be investigated and routine bloods at other visits remain. This is to avoid unnecessary blood draws in healthy children.
10. The list of abbreviations was updated
 11. Section 1.1 Disease setting and Context in the study: updated the first paragraph of this section based on the latest literature.
 12. Section 1.3 Rationale for Trial Population - some spelling errors were corrected
 13. Section 1.4 – Rationale for Choice of Regimen in Intervention and Control Arms. The following updates were made:
 - Phrase “group 5 drugs” replaced with drugs “linezolid and clofazimine.”
 - Section about delamanid was deleted.
 - Use of drug abbreviations corrected.
 - Some spelling errors were corrected
 - Sentence added regarding safety of fluoroquinolones.
 - Additional text was added in justification of using placebo as control arm
 - Clarified that children will also be excluded if they have exposure to both an isoniazid drug-susceptible and an MDR index case
 - Summary added to state value of TB-CHAMP trial and that it is support by WHO
 14. Section 2.1.1 and 2.1.2 – the formatting was corrected.
 15. Section 3 Selection of Patients - Clarification made for who queries about eligibility criteria should be addressed to
 16. Section 3.1 Adult Index Case Inclusion Criteria:
 - Criterion 2 - Clarified that bacteriologically confirmed pulmonary TB diagnosed from a sputum sample, index case having started treatment for MDR-TB within the preceding 6 months. Assessment may be made, on a case by case basis, regarding the risk of the child’s ongoing exposure if the index case is not adherent to treatment or remains infective.
 - Criterion 3 updated to state that confirmation of both rifampicin and isoniazid no longer required
 - Criterion 4 updated to allow close relatives to consent in case where index case deceased
 17. Section 3.2 Child Participant Inclusion Criteria
 - Criterion 1 – wording simplified
 - Criterion 2 – expanded to include significant exposure of child to adult MDR-TB index case

18. Section 3.3 Child Participant Exclusion Criteria
 - Criterion 2 updated to allow for interruption of TB preventive therapy provided the child participant is recruited into the study as soon as possible.
 - Criterion 5 “Children with myasthenia gravis or Guillain-Barré syndrome” was removed
 - A new criterion was added “Weighing below 3 kg”
19. Section 3.4 Number of Household Contacts and Households
 - Sample size reduced to 1009 household contacts, 505 per arm
20. Section 3.5 Co-enrolment Guidelines was deleted
21. Section 3.6 Screening Procedures and Consent
 - Wording updated for clarity and to reflect the changes made to the Schedule of Evaluations.
 - Added that, in general a limit of 6 children to be recruited per household and CTU to be contacted in cases where more than 6 eligible children in 1 household.
 - Definition of significant exposure to MDR TB added
22. Figure 2 updated to clarify child participants must be < 5 years
23. Section 4.1 Enrolment and Randomisation Visit
 - More detail about close relative providing informed consent if the adult MDR-TB index case is deceased.
 - Text updated to improve clarity
24. Section 4.2 Randomisation Practicalities
 - Clarified that the trial statistician holding the randomisation code is unblinded.
25. Section 4.3 Co-Enrolment Guidelines – sentence added stating that referral may be made from the TB-CHAMP team, once a TB end point has been reached, to other therapeutic MDR-TB trials in children.
26. Section 5.1 Introduction to Treatment of Patients
 - Description of study drug (levofloxacin 250mg) was corrected to state that this is film-coated and not dispersible
 - Part of Table 2 was removed
 - Clarification added to describe how dosing changes should be made according to weight of the child
27. Section 5.2 Arm A – Intervention
 - The text has been rearranged and amended for clarity
 - Section 5.2.4 – total treatment duration corrected to 28 weeks and section added about missing individual dosed
 - Section 5.2.6 – words “weekly community based” removed
28. Section 5.3 Arm B – Placebo
 - Section 5.3.1 amount of water IMP may be dispersed in was updated
29. Section 5.4 Overdose of Trial Medication

- Clarified that neuropsychiatric symptoms have rarely been reported
30. Section 5.5 Unblinding
- Wording updated to reflect current CTU unit requirements
31. Section 5.6 Protocol Treatment Discontinuation
- An additional criterion for treatment discontinuation was added:
Relocation to a remote geographic area
32. Section 5.9 Compliance and adherence - Some text amended for clarity.
33. Section 5.11 Co-Enrolment Guidelines deleted
34. Section 6 Assessments and Follow-Up
- Criteria for SAE removed as duplicated later in protocol
 - DAIDS reference table version updated
 - End of trial definition clarified
 - Wording about additional study visits clarified
35. Section 6.1
- Name of section changed from Trial Assessment to Schedule of Evaluations.
 - Section updated to reflect changes in schedule of evaluations listed earlier and the reduced follow-up.
 - Added that Endpoint Review Committee (ERC) will review safety events
36. Section 6.2 Procedures for Assessing Efficacy
- Advice added for reporting TB endpoints
 - Clarifications made to section on assessing incident TB
 - Note added that ERC will also determine the DST of bacteriologically confirmed cases
 - Some spelling errors were corrected
 - The TB end point disease definitions were updated to reflect the international NIH consensus paediatric TB disease, resulting in classifying TB as “confirmed TB”, “unconfirmed TB” and “unlikely TB”). Graham SM, Cuevas LE, Jean-Philippe P, Browning R, Casenghi M, Detjen AK, Gnanashanmugam D, Hesselting AC, Kampmann B, Mandalakas A, Marais BJ, Schito M, Spiegel HM, Starke JR, Worrell C, Zar HJ. [Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update](#). Clin Infect Dis. 2015 Oct 15;61Suppl 3:S179-87. doi: 10.1093/cid/civ581. PMID:
 - Moving forward, the Xpert MTB/RIF Ultra will be used to test respiratory specimens collected in children with signs or symptoms suggestive of TB disease instead of the Xpert MTB/RIF currently used. The Xpert MTB/RIF Ultra is also an automated molecular assay that detects tuberculosis and rifampicin resistance but has improved sensitivity compared to the Xpert MTB/RIF standard version. However, culture remains the most sensitive detection method and will continue to be performed by both liquid (MGIT) and solid culture. All samples will also be stored and both Xpert and Ultra may be completed as needed on all children’s samples with potential TB end points.
37. Section 6.3 Procedures for Assessing Safety

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- Added that safety assessments (clinician assessment of signs and symptoms) will also be completed after completion of treatment, through to week 72.
 - Some minor updates made to wording for clarity
 - Mention of DAIDS updated to 2017
38. Section 6.8 Adherence Assessments
- Wording about weekly community-based treatment support removed
 - Mention of nurse administered questionnaire removed
39. Section 6.10 Early Stopping of Follow-up
- Clarified where to find instructions regarding informing CTU of instances where participants wish to leave the trial
 - Heading for premature study discontinuation updated for clarity.
40. Section 6.13 Assessments at Trial Closure – updated to reflect reduction of follow up to 72 weeks
41. Section 7 Safety Reporting
- subject changed to participant
 - 24 hours changed to one working day
 - Text relating to examination for rash, peripheral neuropathy, tremor, tendonitis and arthralgia occurring at each visit was removed
42. Section 7.1.5 Toxicity
- spelling error corrected
 - number of weeks participants have in order to complete treatment was amended to 28 weeks
 - Advice on discontinuing treatment updated (low threshold to discontinue treatment when signs of tendon pain or inflammation)
 - Sentence added: The risk/benefit of LFX preventive therapy should be considered by the clinical team in the context of a healthy child with MDR-TB exposure and high risk of TB disease progression.
 - Advice on reporting Grade 1 and 2 adverse events updated
43. Section 7.2 Other Notable Events
- New advice to report TB end points as notable events added and “personal injury to the research team during trial implementation” removed
44. Section 7.3 Investigator Responsibilities
- Some details clarified and updated
 - 7.3.1.B Version of DAIDS updated
 - 7.3.1.D Expectedness – Details added for reference safety information added
 - Details of where to submit adverse events updated
45. Section 7.4 MRC CTU Responsibilities
- Updated to reflect that trial physician has been changed
 - Updated to reflect how SUSARs and SARs are reported and annual reports are submitted
46. Sections 8.1 to 8.3

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- Very minor text updates for clarity
47. Section 9.2 Outcome Measures
 - Location of TB definitions added
 - Primary analysis expanded to include possible TB disease
 - Secondary outcomes updated to reflect shortened follow-up
 48. Section 9.3
 - Sample size reduced, explanation provided, and details of calculation updated
 49. Section 9.4 Interim Monitoring and Analysis
 - Details of when interim analysis will take place updated to when at least 500 household contacts have been followed up for at least 24 weeks
 50. Section 9.5 Analysis Plan
 - Note added stating that: Data will be available for the primary analysis after all randomised children have been followed up for at least 48 weeks.
 51. Section 10.1 Qualitative Research
 - Note added stating that: The social science work will be carried out by a dedicated team of social scientists and researchers as described below, based on the availability of additional funding.
 - Spelling errors corrected
 52. Section 10.2 Health Economic Studies
 - Some minor text changes for clarity
 53. Section 10.3 Pharmacokinetics Research – section deleted due to this research being carried out independently to the TB-CHAMP trial
 54. Section 10.4 Diagnostic and Biomarker Substudies
 - Some spelling errors corrected, and minor clarifications made
 55. Section 11 Regulatory and Ethical Issues
 - Some text moved to an alternative section
 56. 11.2.1 reworded for simplification
 - Spelling errors corrected
 - 11.2.2 MCC updated to SAHPRA
 57. Section 11.4 Trial Closure – new section added detailing closure
 58. Section 13 Finance
 - Text amended to reflect how roles and responsibilities are documented
 59. Section 14.4 ERC – spelling error corrected
 60. Appendix 1 Sample Informed Consent Form Adult MDR-TB Index Case updated to reflect changes to protocol and schedule of evaluations

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61. Appendix 2 Sample Informed Consent Form Parental Consent Child updated to reflect changes to protocol and schedule of evaluations
 62. Appendix 3. Template Participant Information Sheet And Consent Form For Pharmacokinetic Study removed as the related section of the protocol was also removed
 63. Appendix 3 was replaced by Deceased Adult Index Consent Form added
 64. Appendix 4: TB case definitions were updated
 65. Appendix 5 Management of toxicities was updated following the MHRA alert for fluoroquinolones.
 66. Appendix 6 IMP dossier was removed

Changes to protocol version 2.0 creating version 3.0, dated 9 February 2021

Summary of Changes

- Other minor spelling corrections, additions and deletion of words, correct labelling of tables, and abbreviations have been incorporated.
- Words to be deleted are noted by ~~striketrough~~ and words or text to be added or corrected in **bold**.

Detailed List of Changes

1. Edits have been made to the summary of trial table as shown below.

Version	~~v2.0~~ v3.0
Date	~~13 May 2019~~ 10 February 2021

- General Information: Funding
- Addition of UNITAID as the funder for TB-CHAMP
- General re-wording for inclusion of 'child/adolescent'
- Change of all font to Calibri
- General addition of participants over 5 and under 17 being eligible if they are IGRA+ regardless of HIV status or if HIV+
- Removal of mention of 100mg formulation of Levofloxacin given the available pharmacokinetics and safety data and the excellent tolerability of this formulation in the trial

2. Trial Registration

- Staff members updated, including CPM, TM and DM from MRC CTU.
- Addition of two co-investigators, Dr Judy Sparg and Dr Suzanne Staples for two additional sites to support timely accrual of the trial
- Addition of preliminary data from other trials, section 1.6

3. Summary of Trial/Trial Schema

- Addition of children aged 5--17 years of age with +IGRA or HIV+ to the trial, previously only under 5s were enrolled
- Clarification that the safety outcome is mortality by 48 and 72 weeks
- Clarification that 1009 children will be enrolled from approximately 505 households

4. Schedule of Evaluations

- Children 5-17 years of age will only be enrolled if IGRA+
- Addition of pregnancy test at baseline for females who have started menses
- Re-addition of week 12 CXR: rationale to avoid missing TB end points in children who do not have well defined symptoms.

- Removal of IGRA at week 24, unless clinically relevant. This is to reduce unnecessary phlebotomy in children
- Removal of safety bloods at weeks 16 and 24. Interim analyses have indicated no safety signal after more than 500 children had been enrolled and followed for 24 weeks.

5. Section 1.3 Rationale for trial population

- This has been updated to include children over 5 as well as under 5.
- The trial had previously included children less than five years of age (regardless of TB infection or IGRA status). Moving forward, the trial will also include children 5-17 years in the household with evidence of TB infection (+IGRA test) or those living with HIV irrespective of TB infection status. Based on the emerging data from a large meta-analysis from observational studies, this group of children have a higher risk of disease progression than previously appreciated, which is similar to the risk observed in all children <5 years of age (with and without a +IGRA). Therefore, older children who are IGRA-positive could potentially be at increased risk of TB progression. The inclusion of this group of children would enhance the generalisability of trial results, while supporting accrual of at-risk children to this trial. Recruitment of older children in the household will offer more benefits for all children in the household and will also improve the recruitment rate of TB-CHAMP, given the challenges to recruit only children < 5 years of age across our current sites.
- Removal of levofloxacin 100mg tablets. The trial is well established using the 250 mg formulation which was prioritised following the PK run-in study which showed higher than expected levofloxacin exposures in children < 5 years of age using the 100 mg formulation. The 250 mg formulation is well tolerated and easy to administer.

6. Section 2: Selection of sites/clinicians

- Addition of two new sites, Tuberculosis and HIV Investigative Network (THINK) and Wits Health Consortium Jose Pearson Hospital (WITS Health) to support recruitment and timely completion of the trial given COVID-19 delays.

7. Section 3.1: Adult Index Case Inclusion Criteria

- Clarification that at least 1 child household contact below the age of 5-18
- Addition of inclusion criterion 4: Genotypic or phenotypic resistance to FQN given the increasing prevalence of fluoroquinolone resistance and the now routine testing of fluoroquinolone resistance in the presence of rifampicin and isoniazid resistance (MDR-TB) in the South African TB programme.

8. Section 3.2: Child Participant Inclusion Criteria

- Child ~~≤5~~<18 years who is a household contact of an adult MDR-TB index case (as stated under adult MDR-TB eligibility criteria).
- Addition of inclusion criterion 5: Assent obtained from any child/adolescent 7 years or older

- Addition of inclusion criterion 6: If ≥ 5 years and < 18 years of age, the child must have a positive IGRA test before enrolment. Note: children < 5 years of age are eligible regardless of IGRA status. All HIV+ children < 18 years of age are eligible regardless of IGRA test status

Assent is required in all children 7 years and older per South African regulatory guidelines. Only children/adolescents with a +IGRA (or HIV+)_will be enrolled given their risk of TB disease progression. A separate assent form is available for children 7-11 years, and for ages 12-17 years.

9. Section 3.3: Child Participant Exclusion Criteria

- Addition of exclusion criterion 6: positive pregnancy test at enrolment. Note: in girls who become pregnant on study, continuation on the study will be allowed.
- Addition of exclusion criterion 7: Participants who are 6 months or less post-partum are ineligible. These women may still be breastfeeding and the levofloxacin breastmilk transfer is unknown.

10. Section 3.4: Number of Household Contacts and Household

- Clarification: A total target of 1009 household contacts (505 per arm) from approximately ~~650~~ 505 randomised households will be enrolled.

11. Section 3.5 Screening Procedures and Consent

- Fourth paragraph, 2nd sentence: Household assessment: In general, up to six children < 5 18 years per household may be recruited. The CTU team should be contacted if there are potentially more than 6 eligible children per household.
- Fifth paragraph, 1st sentence, Home visits will be undertaken and the household and child household contacts with ~~significant~~—significant exposure enumerated.
- Fifth paragraph, 4th sentence, All household members with suggestive symptoms or signs (adults ~~and all children 5 years and older of age~~ 18 years and older) will be referred for TB investigation and TB/HIV care as appropriate, even though adult household contacts ~~and older children~~ are not eligible for the study.
- Eighth paragraph, 1st sentence, Children aged < 5 18 years who were identified as household contacts of the enrolled adult MDR-TB index case during the preceding 6 months will be screened for study entry and eligibility
- Addition of clarification of how recruitment will be implemented to reduce bias in selection of study participants. The study teams at all sites will make multiple attempts to contact every eligible adult index case that has been consecutively referred from local TB services or identified from laboratory extracts. This process diminishes the possibility that any MDR-TB index cases or subsequent contacts are systemically excluded.
- Addition of paragraph about pregnancy, After consenting to screening, a pregnancy test will be performed in any girls who have reached

menses. Girls who have started menses will be advised on how to avoid pregnancy after consultation with the primary caregiver. There are currently no known risks for the use of the investigational medicinal product and pregnancy. However, any female participant found to be pregnant will not be eligible for enrolment onto the trial.

- Clarification regarding assent forms: Assent will also be necessary for children over 7 years, with separate assent forms for 7-11 and 12-18 years given the differences in comprehension and in the risk of pregnancy in children/adolescents aged 12-18 years .
- Addition of a paragraph clarifying the recruitment strategy. The index case, if found to be eligible for the trial, will be approached for verbal permission for the research team to approach their household. This is an essential step as the index case's MDR-TB status would be disclosed by doing this. If consent is not given to approach the household for potential enrolment onto TB-CHAMP, all steps will be taken by the research teams to refer household members to local routine TB services, as per local standard of care. The caregivers or parents of potential TB-CHAMP participants are then given the option of enrolling their child onto the study, with formal written informed consent to be obtained at this point.
- Clarification that household assessments are flexible: the household will be enumerated either in person with a home visit, or at the facility or clinic where the index case has been screened and informed consent signed

12. Figure 3, Overview of Participant Flow updated to allow for participants aged 5-17 with +IGRA result or HIV infection and all children regardless of HIV status.

13. Section 4.1 Enrolment and Randomisation Visit

- Addition of 3rd bullet point, If the child is 7 years old or older, they will also be approached for assent.
- Addition of For all children 5 years and below 18 years old, a positive IGRA test must be obtained before enrolment unless HIV+.
- Addition of A pregnancy test will be performed if the participant is female and has started menstruating. A negative result will need to be obtained before the participant can be enrolled onto the trial.

14. Section 4.2 Randomisation Practicalities

- Third paragraph, 1st sentence, A file of the randomisation list in which the study products are identified will be kept in an electronically secure location at MRC CTU, with ~~off-site~~ offsite back-up.

15. Section 4.4 Guidance for Re-enrolment of child participants

- Addition of information for re-enrolment of participants onto TB-CHAMP if they have previously completed their treatment on the trial. Since

children may have new TB exposure again in the household, this would usually merit a new course of TB preventive therapy.

16. Section 5.1 Introduction

- Table 2 has been updated to include weight bands for older children based on the revised eligibility criteria.
- Removal of 100mg Levofloxacin tablets (refer to section

Table 2. Weight bands for levofloxacin (100 mg and 250 mg tablets) and placebo

Weight bands (kg)		Levofloxacin 250	Placebo 250
3	4.9	0.25	0.25
5	6.9	0.5	0.5
7	9.9	0.5	0.5
10	11.9	1	1
12	15.9	1	1
16	19.9	1.5	1.5
20	24.9	1.5	1.5
25	29.9	2	2
30	30.9	2.5	2.5
≥ 40		3	3

17. Section 5.2, Arm A - Intervention

- Addition of information regarding IMP
- Information about the 100 mg levofloxacin formulation has been removed since it is no longer required for the trial and based on the findings of the pharmacokinetic lead-in study.

18. Section 5.6 Protocol Treatment Discontinuation, change made to text in 8th bullet point

- A diagnosis of a new infectious adult TB case in the household with drug-susceptible-susceptible TB
- Section 5.8 Compliance and Adherence: Study drug will be administered/monitored daily by parents/caregivers with and treatment adherence support will be provided at study visits or between visits as required.
- Addition of withdrawal of assent

19. Section 6, Assessments and Follow Up, addition of information regarding pregnancy at follow up visits

- Pregnancy tests will be carried out at any follow up visit if pregnancy is suspected. If a participant becomes pregnant on the trial, they will be allowed to continue and the pregnancy will also be followed up. In the case of a positive test, MRC CTU at UCL should be notified.

20. Section 6.1 Schedule of Evaluations, readdition of investigations

- A chest radiograph (CXR) in two projections, anterior-posterior (AP) and lateral, should be performed at screening and **week 12 visits. The CXR at week 12 is to ensure that no children with minimal symptoms and abnormal CXR are missed (TB end points).**
- Interferon-Gamma Release Assay (IGRA) will be performed for all patients at screening/enrolment, **with participants aged over 5 and below 18 years only being eligible for the trial with a positive result. IGRA tests can be performed at any point throughout the trial if TB is suspected** in conjunction with other TB investigations.
- Haematology at baseline and then at weeks 8, ~~and 24~~ and if clinically indicated, at additional time points. Given extensive data indicating safety of this regimen in more than 500 children followed for 24 weeks, these additional safety bloods are not required, in consultation with the IDMC.
- Whole blood (PaxGene tubes) and serum stored for biomarker and diagnostic sub studies will be taken with each blood draw (baseline and then at weeks 8, ~~24 and 48~~, and upon reaching a TB end point or early trial exit.
- Stool will be collected (subset of participants **under 5 years of age only at the DTTC site only; nested sub study**), at baseline, week 8, 16, 24, week 48 and upon reaching a TB endpoint or an early trial exit.
- **Pregnancy test at baseline**
- **At baseline and at week 48, HIV testing will be repeated in all HIV-negative participants with appropriate counselling and consent. Participants diagnosed with HIV will be managed as per national South African guidelines.**
- **Gastric aspirates or expectorated sputum in older children**

21. Section 6.1 Schedule of Evaluations, typographical error corrected

- Seventh paragraph, 2nd sentence, {Appendix 4 which defines TB as (bacteriologically) confirmed, unconfirmed and ~~unlikely~~ unlikely TB}

22. Section 6.3 Procedures for assessing safety, updated to correspond with new schedule of evaluations
- Fourth paragraph, 1st sentence, Safety laboratory investigations will be performed at baseline and at week 8 ~~and at 24 weeks~~
23. Section 6.9 Management of Pregnancy, added section to correspond with new information regarding older participants in the study
- **All eligible girls with childbearing potential will be followed up with pregnancy tests at their visits. Any girls who become pregnant on the trial should receive counselling about their options and receive support to make decisions about continuing pregnancy. The pregnancy will be followed up to determine the outcome and status of mother and child. All pregnancies should be reported as notable events, unless they meet the safety reporting criteria of a serious adverse event. There are no safety concerns about the use of the IMP and pregnancy, nor use of oral contraceptives and the efficacy of the IMP.**
24. Section 7.1.5 Pregnancy as a notable event, added section to correspond with new information regarding older participants in the study
- **Pregnancy whilst on the trial should always be reported as a notable event. They do not constitute SAEs unless they result in a condition that meets the seriousness criteria defining SAEs. The clinical team responsible will be informed of the mother's participation in the trial and will be asked to inform MRC CTU at UCL if there is any suspicion of any adverse effect of the trial medication. Adverse events occurring in an infant born to female trial participants within 28 days of delivery should be reported in order to evaluate for a possible adverse reaction related to *in utero* exposure to the study drugs. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the investigational product, should also be reported as an SAE. Any event fulfilling the criteria of an SAE (e.g. congenital abnormality or birth defect) should be reported within 1 working day of them becoming aware of the event. Follow-up of a child born to the partner of a male participant (who was taking trial treatment at the time of conception) will be according to local practice. At the end of pregnancy, the investigator will complete a Pregnancy Outcome CRF.**
25. Section 7.2, other notable events, typographical error corrected
- TB endpoints should be captured on the ~~appropriate~~ **appropriate** CRFs and should be reported within one working day as a notable event. Please also refer to the MOP.-
26. Section 9.2.3 Safety Outcomes
- Clarification the primary safety outcome, adverse events grade ≥ 3 at least possibly associated with study drug during 24 weeks of treatment,

will not be adjudicated by the ERC.

- Addition of adverse event grade ≥ 3 as a secondary safety outcome.
- Removal of adverse events grade 1 and 2 at least possibly associated with study drug during 24 weeks of treatment as a secondary safety outcome.

27. Section 9.2.4 Other Secondary Outcomes, new section with the following previously defined in Safety Outcomes section

- Proportion of LFX or LFX-placebo doses taken by 24-28 weeks
- Incidence of LFX resistance in children from either arm developing culture-confirmed TB.

28. Section 9.2.5 Adherence, addition of further information regarding definition of adequate treatment, which is taking at least 80% of allocated doses by 24-28 weeks of treatment duration.

29. Section 9.3 Sample size, added new section regarding power calculations considerations relating to change in study inclusion criteria:

Change in study inclusion criteria from version 3.0 protocol: considerations for power calculations

The target sample size remains the same following the change in inclusion criteria to include children/adolescents aged 5-17 years old with evidence of TB infection or living with HIV, for the following reasons: We expect the overall mean number of child and adolescent HHCs enrolled per household to be approximately 2.0, consistent with the original assumption. This is because the observed mean up to 1 October 2020 is 1.8, and is expected to increase to 2.5 for enrolments from version 3.0 onwards (corresponding to 30% of all households in the overall study). The overall TB event rate in the control arm is expected to increase slightly with the change in inclusion criteria assuming: (i) 40% of children/adolescents aged 5-17 years are IGRA-positive (ii) the effects of age and IGRA status on risk of TB are consistent with the findings by Martinez *et al.* (ii) LFX efficacy remains 60% among older children/adolescents with evidence of TB infection or living with HIV.

30. Section 9.4 Interim Monitoring and Analysis, information on approach of analysis moved to/clarified in Analysis Plan section.

31. Analysis Plan ~~Data will be available for the primary analysis after all randomized children have been followed for at least 48 weeks. The primary analysis will follow an intent to treat (ITT) principle including all randomized children and all TB cases diagnosed up to week 48 after randomization. A modified ITT (MITT) analysis will also be performed~~

~~which excludes randomized children who are subsequently found to have had TB in the first 30 days following enrolment.~~

- The primary analysis will now be based on modified intention-to-treat (mITT) approach instead of ITT.
- Further information provided for the approach of analysis.
- ~~A generalized linear mixed modelling approach will be used to compare the primary outcome for LFX to LFX placebo, which will include an appropriate random effect to allow for intra household correlation. The primary model will adjust for centre (stratification factor) and if clinically important imbalances in baseline characteristics are observed, will also adjust for these variables.~~

32. Section 12, Indemnity, typographical errors corrected

- The sponsor of the trial is the Stellenbosch University. Stellenbosch University therefore accepts overall responsibility for his trial (~~see sponsor letter of support~~). Clinical trial ~~insurance~~ **insurance** has been ~~obtained~~ **obtained** by the ~~sponsort~~ **sponsor** for all trial ~~participants~~ **participants** at ~~all 3 sites~~ **all trial sites** ~~the existing three sites.~~

33. Section 13, Finance, addition of new funder

- The trial is support by grant funding from **UNITAID**

34. Section 14.4, Endpoint Review Committee, removal of function 3

- ~~To review all grade 3 and 4 events and lower grade events that are judged to be at least possibly associated with LFX~~

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18 APPENDICES

Appendix 1. Template Participant Information Sheet and Consent Form for adult MDR-TB index case

Appendix 2. Template participant Information Sheet and Consent Form for child participants

Appendix 3. Template participant Information Sheet and Consent form deceased adult MDT-TB index case.

Appendix 4. Template participant assent form for child participants over 7-11

Appendix 5. Template participant assent form for participants aged over 12-17

Appendix 6. Parent/Legal Guardian participant information leaflet

Appendix 7. TB Disease Classifications

Appendix 8. Management of specific toxicities

APPENDIX 1. SAMPLE INFORMED CONSENT FORM ADULT MDR-TB INDEX CASE

SHORT TITLE: Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)

INTRODUCTION

You are being asked to take part in this research study because you have tuberculosis (TB) that does not respond to treatment with two of the most important drugs used to treat TB (this type of TB is called multi-drug-resistant tuberculosis, MDR-TB). You have also started TB treatment in the past six months. Because you are sharing or have shared a household with one or more children or adolescents below the age of 18 years who may be at risk for developing TB, we would like to investigate children or adolescents in your household for TB. In this study, you will be known as an “index case”. You will not be taking any drug as part of this research study. You will continue to take your TB drugs as prescribed by your own doctor.

People who have shared the same home with a person with MDR-TB may have become infected with the TB germ. Those who are infected with the TB germ may be feeling well but the TB germ may start to grow and attack the body and make people sick. In people like this, we can treat the TB germ to stop it from making people sick with TB. A normal TB germ can be treated with a medicine called isoniazid taken daily for six months. A TB germ that does not respond to treatment with the two most important drugs can possibly be treated with another medicine called levofloxacin taken daily for six months.

In this study, we want to see whether the drug levofloxacin can keep MDR-TB away in children living with a person who has MDR-TB.

Please note that there is currently no general recommendation on how best to treat children exposed to MDR-TB. This is because no studies (clinical trials) have yet been done. Our study will try to answer this question in South African children.

Levofloxacin is a routine TB medicine that is currently used to treat MDR-TB in children, globally and also in South Africa, and is effective to treat MDR-TB disease. In this study, we want to see whether this medicine, levofloxacin, can also prevent healthy children with a household contact, from getting MDR-TB disease. Young children) have a very high risk of developing TB if they do not receive preventive treatment for TB.

Before you decide if you want to be a part of this study, we want you to know more about this study. This is a consent form. It gives you information about this study. The study staff will also talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy of the signed document to keep.

WHO IS DOING THIS RESEARCH STUDY?

This research study is led by Stellenbosch University, managed by Medical Research Council Trials Unit (MRC CTU) at University College London (UCL), London and funded by UNITAID, the Joint Global Health Trials Scheme of the Department for International Development in the United Kingdom (UK) (DFID), the Wellcome Trust and the Medical Research Council (MRC UK) and the South African Medical Research Council (SA MRC).

This research study has been approved by Research Ethics Committees (REC) in South Africa and the UK; and by all required regulatory authorities including the South African Health Products Regulatory Authority (SAHPRA). Ethics committees are groups of scientific and non-scientific people who review and accept or reject research proposals involving people. They make sure that participants' rights are protected. This study is done in accordance with the guidelines of the International Conference on Harmonization for Good Clinical practice (ICH-GCP) and the Declaration of Helsinki (2013).

This study will be conducted in 3 to 5 South African sites, in Cape Town, Johannesburg, Klerksdorp, Port Elizabeth, Durban and Pietermaritzburg (including adjacent areas).

The doctor in charge of this study at your site is: (insert name of Principal Investigator).

This study will be submitted for WHO ERC approvals.

WHY IS THIS STUDY BEING DONE?

This study is being done to see if:

- Treating children or adolescents living with an adult who has MDR-TB with a drug called levofloxacin will reduce their risk of getting TB compared to treatment with an inactive drug (placebo).
- It is safe to treat children and adolescents living with an adult who has MDR TB with the drug levofloxacin.

There will be two groups of participants in this study:

- Children and adolescents who will receive the drug called levofloxacin daily for 24 weeks;
- Children and adolescents who will receive a placebo (inactive drug) daily for 24 weeks.

WHAT WILL HAPPEN ONCE I AGREE TO BE IN THIS STUDY?

You will be given an individual identification number. Then the study team will approach the parent(s) or guardian(s) of any children or adolescents living in your household. If the parent(s)/guardian(s) agree to take part, the children/adolescents who are sharing a household with you will be randomly allocated to either levofloxacin or placebo by a computer. This is like flipping a coin to decide which treatment will be given. This way all children/adolescents under 18 years in a household will have an equal chance of being allocated to receive either levofloxacin or placebo.

Only one study staff member at the main study centre will know which treatment group the children/adolescents you share a household with belong to and they will

not tell anyone else. This means that neither you, the children/adolescents nor the study staff will know which treatment group the children/adolescents in your household will be in before or during the study.

Levofloxacin is approved by the United States (US) Food and Drug Administration (FDA) and the South African Health Products Regulatory Authority) for treating MDR-TB in adults. It is also routinely used for the treatment of MDR-TB in young children. Levofloxacin is not approved for the prevention of MDR-TB. No rigorous research has yet been done to specifically study this in children/adolescents. The dose of levofloxacin to be used in this study (15-20mg/kg) has been shown to be safe and well tolerated in South African children with MDR-TB. This dose is currently routinely used for the treatment of MDR-TB disease in children/adolescents.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you join this study, you will have 1 study visit conducted by a trained study staff member. The visit may be in your house, the clinic, or another place. The study staff will tell you how long the visit will take.

After you have read and signed this consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study:

- You will be asked questions about your household, your medical history, your TB diagnosis and any medicines you have taken and/or are taking now.
- Your HIV status will be confirmed from medical records. If you have not had an HIV test done, study staff will recommend that you have an HIV test done. You will receive counselling before and after your HIV test.
- If you are infected with HIV, we will check your medical records to see your latest CD4 cell count.
- If your MDR-TB has been confirmed in the laboratory through routine care, then a sputum sample(s) would have been taken at the time and stored by the routine National Health Laboratory Service (NHLS). If one of your child contacts develops TB, the study staff will ask your permission for us to have the stored sample(s), so that we can do some further testing to see if the TB in the child contact(s) is similar to your TB.
- We will also ask your permission to contact the parent(s) or guardian(s) of children/adolescents below the age of 18 years old sharing a household with you. We would like to invite them to participate in this study.

WHAT IF I DO NOT MEET THE REQUIREMENTS TO BE IN THE STUDY?

If you decide not to take part in this study or if you do not meet the requirements to join the study, we may still use some of your TB information collected during the visit. The information may also help researchers understand more about HIV and TB treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1,009 children from 505 households will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will have one study visit. The children/adolescents in your household will be in the study for 18 months.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is stopped or cancelled; and/or
- you are not able to attend the study visit as necessary for the study.

WHAT ARE THE RISKS OF PARTICIPATING IN THE STUDY?

It is possible that participating in this study will make it difficult for you to keep your TB and/or HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your TB or HIV status. Please talk with the study staff if you have any concerns about this.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no direct benefit from taking part in this study. Information learned from this study may help others who risk the possibility of having TB. It is possible that children enrolled from your household may benefit from this study if they receive the study intervention, levofloxacin, and this prevents MDR-TB in children/adolescents.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

The alternative to participation in this study is not to participate.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. This means that we will keep all your personal and medical information secret and will not share anything with people you live with. However, by consenting to this trial you agree that the people in your household will be told that you have MDR-TB. We will not share anything with other people in your community. However, we cannot promise absolute confidentiality. Personal information may be shared if necessary by law, for example when other medical concerns come up. Any publication of this study will not use your name or have information that would identify you personally.

Your medical information and reports may be reviewed by the funders of this study, regulatory authorities, the ethics committees involved, study staff, study monitors, and drug companies supporting this study.

WHAT ARE THE COSTS TO ME?

Taking part in this study will not lead to added costs to you or your medical aid (if relevant).

WILL I RECEIVE ANY PAYMENT?

You will receive payment for travel to and from the clinic for study visits and other expenses.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries at no cost. There will be a program for compensation

through the institution involved in this study. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted and will not result in any loss of benefits that you would otherwise receive. Your decision will not have any impact on you receiving your usual medical treatments.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results at the end of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name and contact details of Ethics Committee

If you have questions about this trial you should first discuss them with the study doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA)

The Registrar
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001
Fax: (012) 395 8126
E-mail: Portia.Nkambule@SAHPRA.gov.za

Please go to the next page to sign.

TB-CHAMP SIGNATURE PAGE ADULT INDEX CASE CONSENT

Signing below shows that you have been informed about participating in this study; that you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has allowed you to make a fully informed and free decision about your participation.

By signing this consent form, you do not waive any legal rights, and the investigator(s) or funder(s) are not relieved of any liability they may have. A copy of this consent form will be given to you.

	Yes	No
I have read/been read the information sheet for the TB-CHAMP study and agree to my household being contacted to assess whether the child/children in the household are eligible to take part in this study.		
I understand that this will involve being seen by the TB-CHAMP study team (counsellors, doctors and nurses) who will ask questions about my household, my health, and the health of the people in my household.		
I agree that my medical records may be accessed by the TB-CHAMP study team to collect information about my TB disease.		

Please sign your name below.

Participant's Name (print) Participant's Signature Date
(dd/mm/yyyy)

Staff Conducting Study Staff's Signature Date
Consent Discussion (print) (dd/mm/yyyy)

Witness' Name (print) Witness' Signature Date
(As appropriate) (dd/mm/yyyy)

*Witness is impartial and was present for the entire consent process.
Retain original Informed Consent Form on file.
Offer participant a copy.
Place a copy in medical records if applicable.

APPENDIX 2. SAMPLE INFORMED CONSENT FORM PARENTAL CONSENT CHILD COMPLETE ONE FOR EACH CHILD/ADOLESCENT IN THE HOUSEHOLD

SHORT TITLE: Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)

INTRODUCTION

You are being asked to let your child/adolescent take part in this research study because your child/adolescent lives or has lived with or had prolonged contact with someone who has tuberculosis (TB) that does not respond to treatment with two of the most important drugs used to treat TB. This type of TB is called multidrug-resistant tuberculosis (MDR-TB).

People who have shared the same home with a person with MDR-TB may have become infected with the TB germ. People who are infected with the TB germ are generally well. The TB germ may, however, start to grow and attack the body and make people, also children, sick. In people who are well but are infected with the TB germ, we can treat the TB germ to stop it from making people sick with TB. A normal TB germ can be treated with a medicine called isoniazid taken daily for six months. A TB germ that does not respond to treatment with the two most important drugs can possibly be treated with another medicine called levofloxacin taken daily for six months.

Please note that there is currently no general recommendation on how best to treat children or adolescents exposed to MDR-TB. This is because no studies (clinical trials) have yet been done. Our study will try to answer this question in South African children and adolescents.

Levofloxacin is a routine TB medicine that is currently used to treat MDR-TB in children/adolescents, globally and also in South Africa, and is effective to treat MDR-TB disease. In this study, we therefore want to see whether this medicine levofloxacin can also protect healthy children/adolescents with a household contact, from getting MDR-TB. Young children (below the age of 5 years) have a very high risk of developing TB if they do not receive preventive therapy for TB. At the moment, we do not know what the best treatment is to give to children who have been exposed to MDR-TB and this is why we are doing the study.

Before you decide if you want your child/adolescent to be part of this study, we want you to know more about this study. This is a consent form. It gives you information about this study. The study staff will also talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child or adolescent to take part in this study, you will be asked to sign this parental consent form. You will get a copy of the signed document to keep.

WHO IS DOING THIS RESEARCH STUDY?

This clinical trial (research study) is led by Stellenbosch University, managed by Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UCL) and is funded by UNITAID, the Joint Global Health Trials Scheme of the Department for

International Development in the United Kingdom (UK) (DFID), the Wellcome Trust and the Medical Research Council (MRC UK) and the South African Medical Research Council (SA MRC).

This research study has been approved by Research Ethics Committees (REC) in South Africa and the UK; and by all required regulatory authorities including the South African Health Products Regulatory Authority (SAHPRA). These ethics committees are groups of scientific and non-scientific people who review and accept or reject research involving people. They make sure that participants' rights are protected. This study is done in accordance with the guidelines of the International conference on Harmonization for Good Clinical practice and the Declaration of Helsinki (2013).

The doctor in charge of this study at your site is: insert name of Principal Investigator

This study will be conducted in 3 to 5 South African sites, in Cape Town, Johannesburg, Klerksdorp, Port Elizabeth, Durban and Pietermaritzburg and surrounding areas.

This study will be submitted for WHO ERC approvals.

WHY IS THIS STUDY BEING DONE?

This study is being done to see if:

- Treating children and adolescents living with an adult who had or has MDR-TB with a drug (medicine) called levofloxacin will reduce their risk of developing TB compared to treatment with placebo (an inactive drug) therapy.
- It is safe to treat children and adolescents living with an adult who has MDR-TB with the medicine levofloxacin.

There will be two groups of participants in this study:

- Children/adolescents who will receive the drug called levofloxacin daily for 24 weeks;
- Children/adolescents who will receive a placebo (inactive drug) daily for 24 weeks.

WHAT WILL HAPPEN ONCE I AGREE THAT MY CHILD PARTICIPATES IN THIS STUDY?

Your child/adolescent will be randomly allocated to receive either levofloxacin or placebo by a computer. This is like flipping a coin to decide which treatment will be given. This way all people under 18 in a household will have an equal chance of being allocated to receive either levofloxacin or the inactive drug (placebo). Neither you, the children or adolescents, or the study staff will know which treatment group the children in your household will be in before or during the study. Only one study staff member at the main research centre will know which group your child/adolescent(s) belong to and they will not tell anyone else. All children/adolescents will receive the same clinical care and the doctors and nurses attending to your child will not know which treatment your child/adolescent is getting.

WHAT DO I HAVE TO DO IF MY CHILD IS IN THIS STUDY?

If you let your child/adolescent participate in this study, your child/adolescent will undergo approximately 9 study visits over 18 months. Some of these visits may be in your house but most will be at the study site. The study staff will tell you how long each visit will take. You may need to bring your child/adolescent to the clinic for additional visits if your child

develops any negative signs or symptoms related to the drug (these are called side effects) or if you are worried that your child has TB.

Your child/adolescent will receive one of the following 2 treatments:

The drug levofloxacin daily for 24 weeks

OR

An inactive drug (placebo) for 24 weeks.

Levofloxacin is approved by the United States (US) Food and Drug Administration (FDA) and the South African Health Products Regulatory Authority (SAHPRA) for treating MDR-TB in adults. It is also routinely used for the treatment of MDR-TB in young children. Levofloxacin is not approved for the prevention of MDR-TB. No rigorous research has yet been done to specifically study this in children/adolescents. The dose of levofloxacin to be used in this study (15-20mg/kg) has been shown to be safe and well tolerated in South African children with MDR-TB. This dose is currently routinely used for the treatment of MDR-TB disease in children/adolescents.

The study tests to be done on your child/adolescent (investigation for TB, some blood tests etc.) are part of routine recommended clinical care in children exposed to MDR-TB. There will be additional tests for diagnostic and biomarker studies which are pure research tests.

Screening Visit

After you have read and signed this consent form, your child/adolescent will have several pre- screening evaluations to make sure that he/she is suitable to participate in the study:

- You and your child/adolescent will be asked questions about his/her medical history and about any medicines he/she has taken or is taking now.
- Your child/adolescent will have a physical examination, and you and your child/adolescent will be asked questions about his/her health, including any symptoms that may suggest TB infection or disease.
- Your child/adolescent will have a blood test done (4ml blood which is less than a teaspoon) to see if he/she is infected with the TB germ.
- If the child/adolescent is female and has begun menstruating, they will have a pregnancy test done.
- If records from previous chest X-rays are available, they will be examined to see if there are any signs that your child/adolescent might have TB. If a recent previous chest X-ray is not available, your child/adolescent will have to have a chest X-ray taken to make sure that your child does not have TB of the lungs.

Entry Visit

If your child/adolescent is found suitable to participate in the study in a safe way, he/she will undergo a study visit by one of the research study staff. At this visit:

- Your child/adolescent will have a physical examination, and you and your child will be asked questions about his/her health, including any symptoms that may suggest TB infection or disease.

Your child's HIV status will be confirmed. If there is no record of a previous HIV test, you will be asked to have a HIV test taken of your child. You will have counselling before and after your child/adolescent is tested for HIV. This is routine in all children investigated for TB. You will be told the result of the HIV test in your child as soon as it is available. If your child is found to

have HIV at this test we will refer him/her for further HIV care.

- If your child/adolescent is living with HIV, we ask permission to check your child's medical records to see the latest results of his/her CD4 count and HIV viral load. If your child/adolescent is HIV-infected, we will draw about 1ml (a few drops) of blood for a CD4 count and HIV viral load test.
- Your child/adolescent will have safety blood tests done, the total volume amounting to about 1ml of blood.

Your child/adolescent may also be asked to have the following tests:

- A stool test.
- About 1 teaspoon (5 ml) of blood drawn and stored for future testing linked to this study (that is in total then about 7ml or 1 ½ teaspoons of blood).

At each following study visit the following will be undertaken:

- Weight, height, and mid-upper arm measurement of your child/adolescent.
- Your child/adolescent's medical history since last visit.
- A physical examination to detect any adverse events (side effects) to the drug and to detect any signs and symptoms that may suggest TB disease. If the staff at your site believe that your child might have TB, he/she will get a chest X-ray and possibly other investigations.
- A doctor or nurse will ask about any changes in the medication your child/adolescent is taking (including HIV treatment if your child is HIV-positive).
- You will be asked about how well your child/adolescent is taking the study medications.
- The staff will teach you about the signs and symptoms of TB in you and your child/adolescent.

At the study visits at 4, 8, 12, 16 and 24 weeks the following will be undertaken:

- At weeks 4, 8, 12, 16 and 24 physical examination, and you and your child/adolescent will be asked questions about his/her health, including any symptoms that may suggest TB infection or disease.
- At weeks 4, 8, 12, 16 and 24 you will be asked about how well your child/adolescent is taking the study medications.
- At any time if the staff believe that your child/adolescent might have TB, your child will be asked to provide some sputum by coughing and then spitting into a cup. Usually in small children under 5 years of age, the study staff will obtain a sample by collecting some stomach content (called a gastric aspiration), since small children have trouble coughing up their phlegm and usually swallow it. A gastric aspirate involves putting a tube through your child's nose and aspirating some sputum from the stomach. Your child's sputum will be used for TB diagnostic tests. This is a routine procedure to investigate TB in young children.
- Stool will be collected at weeks 8, 16, 24 and 48
- At week 24, if your child/adolescent is HIV positive, about 1 ml (less than ¼ teaspoon) of blood will be drawn extra to get the CD4 count and HIV viral load.
- If the results are abnormal you will them as soon as they are available. If they are normal you will receive them at the next study visit.
- The staff will teach you about the signs and symptoms of TB in you and your child.
- If your child/adolescent begins menstruation whilst on the trial, they may be asked to do a pregnancy test.

At the study visits at 48 and 72 weeks the following will be undertaken:

- At week 48 and if your child/adolescent's HIV test was negative before, another HIV test will be requested for your child/adolescent. You may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available.
- At weeks 12 and 48 a chest X-ray will be taken.
- At week 48 and 72, if your child/adolescent is HIV positive, about 1 ml (less than a ¼ teaspoon) of blood will be drawn to get the CD4 count and HIV viral load.
- The staff will teach you about the signs and symptoms of TB in you and your child/adolescent.

Evaluations if we are worried that your child may have TB

If you believe that your child/adolescent has developed TB while participating in the study, please contact the study staff as soon as possible. Your child/adolescent will be asked to come to the research clinic for the following evaluations:

- If your child/adolescent's HIV test was negative, another HIV test will be done. You may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available.
- Your child/adolescent will have a physical examination and will be asked questions about his/her health, including any medications received and symptoms which may suggest TB disease.
- Your child/adolescent will have a chest X-ray
- Your child/adolescent will be asked to provide some sputum either by coughing or from a gastric aspirate (see earlier description). If we find the TB bacterium in the sputum, we would do more testing to see if the bacterium is susceptible to TB medications. Your child/adolescent's sputum sample would also be stored for future use and further TB testing.

Evaluations that will be done if your child leaves the study early

If you want your child/adolescent to leave the study before he/she has finished all of the study visits, you will be asked to bring your child/adolescent to the clinic for the following evaluations:

- Your child/adolescent will have a physical examination and you will be asked questions about his/her health, including any medicines and symptoms that may suggest TB infection or disease.
- Your child/adolescent will have a chest X-ray (and other relevant investigations).
- About 5 ml (1 teaspoon) of blood will be collected

Once your child/adolescent exits the study, they will no longer be able to receive study drug.

If your child/adolescent is not enrolled into the study after the screening visit

If you decide not to let your child/adolescent take part in this study or if your child does not meet the requirements to join the study, some of his/her medical and clinical information collected during the screening visit will still be used. This information may be used by researchers to help determine whether there are patterns or common reasons why people do not join a study. The information may also help researchers understand more about TB treatment and HIV. You will be referred back to your clinic.

If your child/adolescent becomes pregnant on the study

There will be pregnancy tests for any girl who begins her periods (menstruation) during the study. These are just to make sure the trial team is being as safe as possible. If a participant becomes pregnant on the study, they will be given the option to continue with the treatment. If they do not wish to do so, they will still be followed up through study visits.

Important message

If your child/adolescent starts to cough, sweats a lot at night, starts to lose weight or does not gain weight as expected, develops a fever, becomes sleepy or less playful, or develops swelling in the neck, you should contact the study team as soon as possible. Please contact the study staff if you have any concerns about your child having TB.

Extra blood sample to store

New tests to diagnose TB are being developed all the time. We therefore ask for your permission to use some of your child/adolescent's blood samples in future for tests that are relevant to TB. This might be during this study or after it ends. These tests would be decided by a group of experts. The blood samples taken from your child/adolescent would never be identified by his or her name.

Samples collected from your child/adolescent may be stored in South Africa or overseas. These samples may be stored for an indefinite period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on your child/adolescent's stored specimens at any time. If you withdraw your consent the specimens will be thrown away. No matter what you decide, it will not affect your child/adolescent's participation in the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1,009 children from 505 households and their children will take part in this study.

HOW LONG WILL I BE IN THIS STUDY FOR?

If you agree that your child/adolescent may participate in the study, your child/adolescent will be in the study for 18 months. In the first year there will be 8 visits and in the second year, only 1 visit.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child/adolescent off the study early without your permission if:

- the study is stopped or cancelled; and/or
- you are not able to attend the study visits as necessary for the study.

The study doctor may also need to take your child/adolescent off the study without your permission if:

- continuing the study may be harmful to your child/adolescent;
- your child/adolescent needs a treatment that you may not take while on the study;
- your child/adolescent is unable to take the study medication as necessary for the study.

If your child/adolescent must stop taking the study drug before the study is over, the

study doctor may ask your child/adolescent to continue to be part of the study without taking the study drug and return for some study visits and procedures.

If your child/adolescent must permanently stop taking study-provided levofloxacin or placebo before his/her study participation is over, the study staff will discuss other options that may be available to your child/adolescent.

WHAT ARE THE RISKS OF THE STUDY TO YOUR CHILD?

The medicine used in this study, levofloxacin, may have negative effects (side effects), which are listed below. Please note that these lists do not include all the side effects seen with levofloxacin. In general, in children/adolescents who receive levofloxacin for the treatment of MDR-TB, have very few side effects and tolerate this medicine well. Below you will find a list which includes the more serious or the more common side effects that may possibly be related to levofloxacin. If you have questions concerning side effects, please ask the study team. If your child/adolescent develops any side effects you should contact the study team immediately.

There is a risk of serious side effects when non-study medications (i.e. other medicines prescribed by someone else) are taken with the study medication. For your child's safety, you must tell the study doctor or nurse about all medications your child is taking before they start the study and also before starting your child/children on any new medications while on the study. Also, you must tell the study doctor or nurse before your child participates in any other research studies (for example clinical trials with drugs) while on this study.

Reported side effects of levofloxacin

- Nausea
- Vomiting
- Dizziness
- Headache
- Trouble sleeping
- Diarrhoea
- Joint pain or swelling
- Tendon pain or swelling
- Muscle pain
- Hallucinations

Risks of Drawing Blood

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, light-headedness, and in rare cases, fainting or infection. The total amount of blood taken at each study visit and in total, over the whole study, is quite small.

Risks of Chest X-ray

The amount of high-energy radiation used in a chest x-ray is relatively small and does not pose any significant risk to your child.

Risks of Social Harm

It is possible that participating in this study will make it difficult for you to keep your or your child/adolescent's HIV or TB status secret from people close to you. This may lead to unwelcome discussions about or reactions to your or your child/adolescent's HIV or TB

status. Please talk with the study staff if you have any concerns about this.

ARE THERE BENEFITS TO MY CHILD TAKING PART IN THIS STUDY?

If you let your child/adolescent take part in this study, there may be a direct benefit to your child, in that they may be less likely to get MDR-TB, but no guarantee can be made. It is also possible that your child/adolescent may receive no benefit from being in this study. Information learned from this study may help others who risk the possibility of having TB.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study you and your child/adolescent have the choice of:

- preventive therapy with routine prescription drugs available to your child;
- no preventive therapy for your child/adolescent.

Please talk to your doctor about these and other choices available to your child/adolescent. Your doctor will explain the risks and benefits of these choices. As previously outlined, there are no international guidelines on how best to treat children exposed to MDR- TB.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your child/adolescent's personal information confidential. This means that we will keep all your child/adolescent's personal and medical information secret and will not share anything with people you live with or with other people in your community. However, we cannot promise absolute confidentiality. Personal information may be shared if necessary by law. Any publication of this study will not use your child/adolescent's name or have information that would identify your child/adolescent personally.

Your child/adolescent's medical information and reports may be reviewed by the funders of this study, the ethics committees, the regulatory authorities involved, study staff, study monitors, and drug companies supporting this study.

WHAT ARE THE COSTS TO ME?

Taking part in this study will not lead to added costs to you and your medical aid (if you have a medical aid).

WILL I RECEIVE ANY PAYMENT?

You will receive payment for transportation and other expenses.

WHAT HAPPENS IF MY CHILD/ADOLESCENT IS INJURED?

If your child/adolescent is injured as a result of being in this study, he/she will be given immediate treatment for his/her injuries. You or the local health service will not bear the cost of any treatment of any injury related to your child/adolescent participating in this trial. Your child will be insured through formal clinical trial insurance. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY CHILD/ADOLESCENT'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to let your child/adolescent take part in this study or take your child/adolescent out of this study at any time. Your decision will not have any impact on your child/adolescent's participation in other studies and will not result in any punishment or loss of benefits that your child would

otherwise receive. Your decision will not have any impact on you receiving your usual medical treatments.

We will tell you about new information from this or other studies that may affect your child/adolescent's health, welfare, or willingness to stay in this study. If you want the results of the study, please let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- Name and contact details of Ethics Committee

If you have questions about this trial you should first discuss them with the study doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA).

The Registrar
South African Health Products Regulatory Authority
Department of Health Private Bag X828
PRETORIA 0001
Fax: (012) 395 8126
E-mail: Portia.Nkambule@health.gov.za

Please go to the next page to sign.

TB-CHAMP SIGNATURE PAGE PARENTAL CONSENT CHILD

Signing below shows that you have been informed about your child/adolescent's participation in this study; that you voluntarily agree for your child/adolescent to participate; that you have asked any questions about the study that you may have; and that the information given to you has allowed you to make a fully informed and free decision about your child's participation.

By signing this consent form, you do not waive any legal rights. Also, the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be given to you.

	YES	NO
I have read/been read the information sheet for TB-CHAMP study and agree to my child participating in the TB-CHAMP study. I understand that my child/adolescent's participation is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child/adolescent's medical care or legal rights being affected.		
I understand that sections of any of my child/adolescent's medical notes may be looked at by responsible individuals involved in the running of the study or from regulatory authorities where it is relevant to my child/adolescent's participation in this research. I give permission for these individuals to have access to my child's records, but understand that strict confidentiality will be maintained.		
I understand that my child/adolescent will receive either levofloxacin or placebo for 24 weeks, but that I and my child and the study team will not know which treatment they are taking.		
Consent for stored samples	YES	NO
I agree to allow samples to be taken from my child/adolescent and for my child's samples (sputum, blood, stool) to be stored for later testing, including genetic testing. I understand that these results and samples will not be identified by either my or my child's name and that I may not be given the results of tests performed on stored samples.		

Please sign your name below.

Participant's Name (print)

**Participant's date of birth
(dd/mm/yyyy)**

**Parent/ Legal Guardian (print)
(As appropriate)**

Parent/Legal Guardian's Signature

**Date
(dd/mm/yyyy)**

**Staff Conducting
Consent Discussion (print)**

Study Staff's Signature

**Date
(dd/mm/yyyy)**

**Witness' Name (print)
(As appropriate)**

Witness' Signature

**Date
(dd/mm/yyyy)**

*Witness is impartial and was present for the entire consent process.

Retain original Informed Consent Form on file.

Offer participant a copy.

Place a copy in medical records if applicable.



APPENDIX 3. INFORMED CONSENT FORM: FOR RELATIVE OF DECEASED ADULT MDR-TB INDEX CASE

SHORT TITLE: Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)

INTRODUCTION

Good day, my name is _____. I am a researcher at the _____.

My condolences on the death of _____. I understand that the death of your relative may have affected you deeply. If you do not want to talk to us we will not bother you during this difficult time. Please let me know if I can continue.

If you do feel able to discuss your relative being in a study we would like to ask you if you are willing

1. to allow us to contact the household of _____ (name of index case). This is to see if they would be interested in allowing household members under the age of five years to be considered to be part of the TB CHAMP study.
2. If we can use the clinic hospital and other health data of your deceased relative.

If you would like to hear more about this study, we will explain it to you before you decide to agree.

We are asking you to allow us to contact the household because your recently deceased relative had tuberculosis (TB) that does not respond to treatment with two of the most important drugs used to treat TB (this type of TB is called multidrug-resistant tuberculosis, MDR-TB). Your relative was diagnosed or started on TB treatment for this type of TB in the past six months. We also understand that your deceased relative shared, or shared a household before, with one or more children below the age of 18 years who may themselves be at risk for developing MDR TB.

We are asking you to allow us to go to the household of the deceased person because

1. you are a close relative of the deceased person (you should be one of the following: a brother or sister of the deceased; are married to, or have lived together with the deceased or have taken at least part responsibility for decisions in the household for at least six months; or are the mother or father, or are an adult child of the deceased)
2. you also live in the household of the deceased index patient or you were named by the deceased as a contact person, or their next of kin.
3. you are 18 years of age or older.

If you agree to the study, we would like to go to your household to check if any children in the household have TB. If they do not have TB, we would ask to include them in a study to prevent drug resistant TB in young children. In this study, the adult person with TB is known as an "index patient" or "index case".

People who have shared the same home with a person with MDR-TB are called contacts and may have become infected with the TB germ. People who are infected with the TB germ are usually not sick. The TB germ may, however, start to grow and attack the body and make people sick. In people who are well but are infected with the TB germ, we can treat the TB germ to stop it from making people sick with TB later. A normal TB germ can be treated with a drug (medicine) called isoniazid taken daily for six months. A TB germ that does not respond to treatment with the two most important TB drugs may possibly be successfully treated with another drug called levofloxacin taken daily for six months. We think levofloxacin works to prevent future TB in people infected with drug resistant TB but do not know for sure. The best way to find this out is to test levofloxacin in patients. In this study, we want to see whether the drug levofloxacin can prevent MDR-TB in children living with a person who has MDR-TB.

Please note that there is currently no clear recommendation on how best to treat children exposed to MDR-TB. This is because no studies (clinical trials) have yet been done. Our study will try to answer this question in South African children.

Levofloxacin is a routine TB drug (medicine) that is currently used to treat MDR-TB in children, globally and also in South Africa, and is effective to treat MDR-TB disease. In this study, we therefore want to see whether this drug (medicine) levofloxacin can also protect healthy children with a household contact, from getting MDR-TB. Young children (below the age of 5 years) have a very high risk of developing TB if they do not receive preventive therapy for TB. At the moment, we do not know what the best treatment is to give to children who have been exposed to MDR-TB and this is why we are doing this study. Before you decide if you agree for us to go to your household and then ask the parents of any children at the house to agree to be in the study, we want you to know more about our study.

This is a consent form. It gives you information about this study. The study staff will also talk with you about this information. You are free to ask questions about this study at any time. If you agree for the household to take part in this study, you will be asked to sign this consent form. You will get a copy of the signed document to keep.

2. WHO IS DOING THIS RESEARCH STUDY?

This research study is led by Stellenbosch University and funded by UNITAID, the Joint Global Health Trials Scheme of the Department for International Development in the United Kingdom (UK) (DFID), the Wellcome Trust and the Medical Research Council (MRC UK) and the South African Medical Research Council (SA MRC). Stellenbosch University has delegated the overall trial management of TB-CHAMP to the Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UCL), London.

This research study has been approved by Research Ethics Committees (REC) in South Africa and the UK; and by all required regulatory authorities including the South African Medicines Control Council (MCC). These ethics committees are groups of scientific and non-scientific people who review and accept or reject research involving people. They make sure that participants' rights are protected. This study is done in accordance with the guidelines of the International Conference on Harmonization for Good Clinical practice (ICH-GCP) and the Declaration of Helsinki (2013). This study will be submitted for WHO ERC approvals.

This study will be conducted in three to five South African sites, in Cape Town, in Johannesburg, Klerksdorp, Port Elizabeth, Durban and Pietermaritzburg (including its surrounding areas).

The doctor in charge of this study at your site is: **Prof Anneke Hesseling**.

3. WHY IS THIS STUDY BEING DONE?

This study is being done to see if:

- Treating children who lived in the same house as an adult with MDR-TB with a drug called levofloxacin will reduce their risk of developing TB compared to treatment with an inactive drug (placebo).
- It is safe to treat children living with at an adult who had or has MDR TB with the drug levofloxacin.
- There will be two groups of children in this study:
- Children who receive the drug called levofloxacin daily for 24 weeks;
- Children who receive a placebo (a placebo has no active treatment and is to make sure that we have a group that did not receive levofloxacin but still received a tablet to compare against) daily for 24 weeks.

4. WHAT WILL HAPPEN ONCE I GIVE CONSENT FOR THE STUDY?

We will go to the household of the children who were sharing a house with the deceased. If their parents (or guardians) agree for them to be in the study, the children will be randomly allocated to either levofloxacin or placebo by a computer. This is like flipping a coin to decide which treatment will be given – but we will not know and you and your family will not know which treatment the child gets. This way all households will have an equal chance of being allocated to receive either levofloxacin or placebo. Only one study staff member at the office will know which treatment group the children belong to and they will not tell anyone else. Neither you, the children nor the study staff will know which treatment group the children in your household will be in before or during the study.

5. WHAT DO I HAVE TO DO IF I GIVE CONSENT FOR MY DECEASED RELATIVE'S HOUSEHOLD TO BE IN THIS STUDY?

If you do agree that your deceased relative's household be contacted to be in this study, and after you have read and signed this consent form, we do a few things to get more detail about the deceased person:

- You will be asked questions about the deceased index case (Relative) medical history, TB diagnosis and any medicines they might have taken.
- We will look at your deceased relative's medical records and take data about the HIV status of the deceased person and also his/her TB treatment previously and other medical tests and treatment before they died.
- If your deceased relative's MDR-TB was confirmed in the laboratory through the clinic or hospital, then a sputum sample or samples would have been taken at the time and stored by the routine National Health Laboratory Service (NHLS). We ask that you agree to allow us to use this specimen that was used to diagnose your relative. If you agree then we will go and find the specimen and use it in the study.

This study process will take about an hour of your time and we will not need to talk to you again after you have provided this information. If you are the parent or guardian of a child under eighteen in the household then we will ask you to provide a separate consent for the child to be in the study.

If you want to know the HIV status of your relative we will arrange for counselling for you before we discuss these results and will also offer to provide HIV testing for you – this will not be for any study purpose and you will have to agree to HIV testing separately. If you are infected with HIV and are not already taking antiretroviral therapy, we will refer you to the nearest clinic – this will not be used for any study purpose. Also if you want to be checked for TB we will refer you to your local clinic for testing.

Your signature below will be your agreement that we can contact the household and speak to parents of children below the age of 18 years old who shared the household with the deceased person. We will then invite them to consider allowing their children to be in this study.

6. WHAT IF MY DECEASED RELATIVE DOES NOT MEET THE REQUIREMENTS TO BE IN THE STUDY?

If you decide not to take part in this study or if your deceased relative does not meet the requirements to join the study, we may still use some of your deceased relative's TB information collected during the visit. The information may also help researchers understand more about HIV and TB treatment.

7. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1,556 children from 505 households will take part in this study at the three sites.

8. WHAT ARE THE RISKS OF PARTICIPATING IN THE STUDY?

It is possible that participating in this study will make it difficult for you to keep your relative's TB and/or HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your relative's TB or HIV status. Please talk with the study staff if you have any concerns about this.

9. ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no direct benefit from taking part in this study. Information learned from this study may help others who are at risk of having TB. It is possible that children enrolled from your household may benefit from this study if the study intervention, levofloxacin, prevents MDR-TB in children.

10. WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

The alternative to participation in this study is not to allow the household to participate.

11. WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your deceased relative's personal information confidential. This means that we will keep all his or her personal and medical information secret and will not share anything with the people you live with. However, by consenting to this trial you agree that the people in your household will be told that your deceased relative had MDR-TB. We will not share anything with other people in your community. However, we cannot promise absolute confidentiality. Personal information may be shared if necessary by law, for example when other medical concerns arise. Any publication of this study will not use your name or have information that would identify you personally.

Your deceased relative's medical information and reports may be reviewed by the funders of this study, the ethics committees involved, study staff, study monitors, and drug companies supporting this study.

12. WHAT ARE THE COSTS TO ME?

Taking part in this study will not lead to added costs to you or your medical aid (if relevant).

13. WILL I RECEIVE ANY PAYMENT?

You will receive a single payment for travel as determined by the South African Health and Related Products Authority (SAHPRA).

14. WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Agreeing for us to use your deceased relative information and agreeing that we can visit the household is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on any treatment you may need at this or other health clinics or hospitals.

15. WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Telephone number **082 658 3030 or 081 880 6535 (24 hour emergency number)**_____

For questions about your rights as a research participant, contact:

- **Mr. Ashwin Manuel (Health Research Ethics Committee of Stellenbosch University) - 021 9389677 or 021 9389140**

If you have questions about this trial you should first discuss them with a study staffer. If you feel you cannot speak to a study staffer, please contact the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Registrar

South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 8126

E-mail: Portia.Nkambule@health.gov.za

Please go to the next page to sign

TB-CHAMP SIGNATURE PAGE: RELATIVE OF DECEASED ADULT INDEX CASE CONSENT

Signing below shows that you have been informed about your deceased relative being included in this study; that you voluntarily agree that we can visit the household to check if the parents of any children at that household may agree to participate in the study. Your signature also means that you have asked any questions about this study that you may have; and that the information given to you has allowed you to make a fully informed and free decision about your participation.

By signing this consent form, you do not waive any legal rights, and the investigator(s) or funder(s) are not relieved of any liability they may have. A copy of this consent form will be given to you.

	YES	NO
I have read/been read the information sheet for the TB-CHAMP study and agree to my household being contacted to assess whether the child/children in the household are eligible to take part in this study.		
I understand that this will involve being seen by the TB-CHAMP study team (doctors and nurses) who will ask questions about my household, and the health of the people in my household.		
I agree that medical records of my deceased relative may be accessed by the TB-CHAMP study team to collect information about their TB disease.		
Consent for stored samples		
I agree to allow any sputum sample(s) of my deceased relative that are stored by NHLS to be retrieved for further testing to see if the TB in the child contact(s) is similar to my deceased relative TB. I understand that these results and sample(s) will not be identified by the name of my deceased relative (after they are retrieved) and that I will not be given the results of tests performed on stored samples.		

Please sign your name below.

**Deceased
Participant Name
and Surname
(Print)**

**Deceased
Participant Date
of Birth**

Relative (of deceased) Name and Surname (Print)	Signature or Mark or Thumb Print	Date
Clinic Staff conducting consent discussion Name and Surname (Print)	Clinic Staff Signature	Date (dd/mmm/yyyy)

**For participants who are unable to read or write or require a translator, also complete the signature block below:*

*Witness' Name and Surname (Print)	Witness' Signature	Date	Time
---	---------------------------	-------------	-------------

**Witness is impartial and was present for the entire consent process.
Retain original Informed Consent Form on file. Offer participant a copy.
Place a copy in medical records if applicable.*

APPENDIX 4. SAMPLE INFORMED CONSENT FORM ASSENT FOR CHILDREN IN THE HOUSEHOLD (7-11 years)

Note: To be administered to children between 7 years to 11 years (inclusive), in addition to parental informed consent.

SHORT TITLE: Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)

Introduction

Hello. We are asking you to join a research study. Research is something people do to find out more about things. In this case we want to find out more about how we can protect children against TB.

1. What is this study about?

This study is called TB-CHAMP. We are looking at children who are living with someone who has a form of TB which needs special types of medicines to treat. This type of TB is called multidrug-resistant tuberculosis (MDR-TB).

The reason we are asking you to be part of this study is because you have been living with an adult (grownup) who has multidrug-resistant tuberculosis (MDR-TB) and we are doing this study to find out more about how best to stop children from getting this kind of TB.

2. Who will be in the study?

About 1000 (one thousand) children younger than 18 years of age will be part of this study.

3. Who is doing this study?

The TB-CHAMP study is led by Stellenbosch University. Different groups in South Africa are part of this study all over the country: Cape Town, Johannesburg (Wits University), Klerksdorp (Wits University), Port Elizabeth (Wits University), and Durban and Pietermaritzburg (THINK).

This study will be submitted for WHO ERC approvals.

Before you decide if you want to be part of this study, we want you to know more. This is an assent form. It gives you information (facts) about this study. We will also talk to you more about this study. You are free to ask questions at any time. If you agree to be part of TB-CHAMP, we ask you to write down your name at the end of this form.

4. How do people get TB?

People who share the same home with a person with TB may get infected with the TB germ. Most people do not get sick when their body gets infected with this TB germ. But children have a higher chance of getting sick (feeling sick, coughing, having fever) with TB.

In this study, we want to see if a TB medicine called levofloxacin, can protect children from getting MDR-TB. There is not yet much information about how to protect children against MDR-TB.

5. What will happen to me if I am part of this study?

You will get one of two types of medicine for 6 months. This will be the medicine levofloxacin, or a “placebo”. A placebo looks and tastes like a medicine, but is like a sugar pill. The computer will choose which one of the two treatments you get. The study team who are working with you will not choose or know which you get. The computer chooses one or the other treatment “randomly”. This is like flipping a coin.

We will see you about 9 study times over one and a half years. Mostly these visits will be at the study clinic but some may be in your house. In the 6 months that you are getting the study medicine, we will usually see you once a month. At each visit we will check how you are growing and whether you are well.

6. What kinds of test will I have if I am part of this study?

We will start off by taking a spoonful of blood to see if your body has “seen” (been infected with) the TB germ. This test is called an IGRA. If your test is positive and you are well, you will be asked to be part of the study. If you have a positive test it does not mean that you are sick with TB. It only means that you saw or were infected with TB before, but didn’t get sick. We will also take a photograph of your chest (chest x-ray). At some visits we will take a small amount of blood (about a teaspoonful full) to check that there are no side effects. We will also store some blood to do tests to check the body’s response to the TB germ.

If we are worried at any stage that you are sick, we will do more tests like taking a sputum sample and doing a chest x-ray. If your parents are worried about you, they will be able to contact us at any time.

7. Can bad things happen to me if I am part of this study?

The medicine used in this study, levofloxacin, can have bad effects (side effects). We do not see these effects often in children. If you have questions about such effects, please ask us about this. If there is anything that is worrying you, please tell your parents immediately.

Some bad things that you could feel are:

- Nausea (feeling like you want to throw up)
- Vomiting (throwing up)
- Dizziness (feeling like you are spinning)
- Headache
- Trouble sleeping
- Runny tummy (diarrhoea)

- Sore joints or swollen joints
- Tendon pain or swelling
- Sore muscles
- Seeing or hearing things that are not really there (hallucinations)

When we take blood, it will not be more than a teaspoon full. We will put some cream on your skin so that the needle does not hurt too much when we take blood.

8. Can good things happen to me if I am part of this study?

People may have good things happen to them because they are in a study. These things are called “benefits.” You yourself may not benefit from being part of this study but, the new information we will get from the TB-CHAMP study will help to find out the best way to protect children against getting TB in the future. We also hope that the medical treatment and care you have in this study will help you and your family.

9. Do I have to be part of this study?

No, you do not have to be part of this study. You can also go to the government TB clinic in your local community for care. You can decide not to be to be part of this study. You can also tell us any time if you do not want to be part of this study any more.

10. Will my information be kept private (confidential)?

Yes, we will keep your information like your name, your parents’ or caregiver’s name, date of birth and so on, private. This means that we will not share it with other people.

11. Who should I ask if I have any questions about the study?

If you have any questions about this study, please tell your parent to call [site contact
_____ on telephone number _____

If you have questions about your rights as a person who is in this study or about things that may have hurt you because you were in this study, please tell your parent to contact [chairperson of local ethics committee] on telephone number _____

Please sign your name and surname on the next page if you agree to be part of this study.

TB-CHAMP SIGNATURE PAGE CHILD ASSENT

Signing below shows that you have been told about this study and that agree to be part of this study.

Please tick off each of the boxes below if you agree.

I agree that I have read/ been read this assent form (<i>insert version no and date</i>) for the TB-CHAMP study and that I understand what is needed of me.	
The study has been explained to me.	
I have been able to ask questions about this study.	
My questions have been answered.	
I understand that I can choose for myself if I want to or don't want to be part of this study.	
I agree to take part in the TB-CHAMP study	

Please sign your name below.

_____	_____	_____
Participant's Name (print)	Participant's date of birth (dd/mm/yyyy)	Participant's signature
_____	_____	_____
Parent/ Legal Guardian (print) (As appropriate)	Parent/Legal Guardian's Signature	Date (dd/mm/yyyy)
_____	_____	_____
Staff Conducting Consent Discussion (print)	Study Staff's Signature	Date (dd/mm/yyyy)
_____	_____	_____
Witness' Name (print) (As appropriate)	Witness' Signature	Date (dd/mm/yyyy)

**Witness is impartial and was present for the entire consent process.*

Retain original Informed Consent Form on file. Offer participant a copy.

Place a copy in medical records if applicable.

APPENDIX 5. SAMPLE INFORMED CONSENT FORM ASSENT FOR CHILDREN IN THE HOUSEHOLD (12-17 years)

Note: To be administered to children between 12 and 17 years (inclusive), in addition to parental informed consent.

SHORT TITLE: Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP)

Introduction

Hello. We are asking you to join a research study. Research is something people do to find out more about things. In this case we want to find out more about how we can protect children against TB.

12. What is this study about?

This study is called TB-CHAMP. This is a study of preventing (avoiding getting) TB. We are looking at children who are living with someone who has a form of TB which ordinary medicines do not treat so well. This kind of TB needs different medicines to treat it. It is called multidrug-resistant tuberculosis (MDR-TB).

The reason we are asking you to be part of this study is because you have been living with an adult who has tuberculosis (TB).

We are doing this study to find out more about how best to stop children and adolescents from getting TB if they live with someone with MDR-TB.

13. Who will be in the study?

About 1000 (one thousand) children who are younger than 18 years of age will be part of this study.

14. Who is doing this study?

The TB-CHAMP study is led by Stellenbosch University. Different groups in South Africa are part of this study all over the country: Cape Town, Johannesburg (Wits University), Klerksdorp (Wits University), Port Elizabeth (Wits University), and Durban and Pietermaritzburg (THINK).

This study will be submitted for WHO ERC approvals.

Before you decide if you want to be part of this study, we want you to know more. This is an assent form. It gives you information (facts) about this study. We will also talk to you more about this study. You are free to ask questions at any time. If you agree to be part of TB-CHAMP, we ask you to write down your name at the end of this form.

15. How do people get TB?

People who share the same home with a person with TB may get infected with the TB germ. Most people do not get sick when their body gets infected with this TB germ. But

children have a higher chance of getting sick (feeling sick, coughing, having fever) with TB.

In this study, we want to see if a TB medicine called levofloxacin, can protect children from getting MDR-TB. There is not yet much information about how to protect children against MDR-TB (where the usual medications do not work so well).

16. What will happen to me if I am part of this study?

You will get one of two types of medicine for 6 months. This will be the medicine levofloxacin, or a “placebo”. A placebo looks and tastes like a medicine, but is like a sugar pill. The computer will choose which one of the two treatments you get. The study team will not choose or know which you get. The computer chooses one or the other treatment “randomly”. This is like flipping a coin.

We will see you about 9 study times over one and a half years. Mostly these visits will be at the study site but some may be in your house. In the 6 months that you are getting the study medicine, we will usually see you once a month. At each visit we will check how you are growing and whether you are well.

17. What kinds of test will be done on me if I am part of this study?

We will start off by taking a spoonful of blood to see if your body has “seen” (been infected with) the TB germ. This test is called an IGRA. If your test is positive and you are well, you will be asked to be part of the study. If you have a positive test it does not mean that you are sick with TB. It only means that you infected with TB before, but didn’t get sick. We will also take a photograph of your chest (chest x-ray). At some visits we will take a small amount of blood (about a teaspoonful full) to check that there are no side effects. We will also store some blood to do tests to check the body’s response to the TB germ.

If we are worried at any stage that you are sick, we will do more tests like taking a sputum sample and doing a chest x-ray. If your parents are worried about you, they will be able to contact us at any time.

If you are a girl and have started having your periods, we will also do a pregnancy test at the beginning of the study and at follow up visits. This will just use urine and will be very quick.

We will also give you advice about ways to not get pregnant. This can be a quick chat about contraception and will be part of follow up visits. Please ask us questions about this at any time.

If at you become pregnant while you are part of the study, please tell us immediately. You can choose to stay on the study or go off the study. You can also to choose to stay on the study but not get the treatment part of the study.

18. Can bad things happen to me if I am part of this study?

The medicine used in this study, levofloxacin, can have bad effects (side effects). We do not see these effects often in children. If you have questions about such effects, please ask us about this. If there is anything that is worrying you, please tell your parents immediately.

Some bad things you could feel are:

- Nausea (feeling like you want to throw up)
- Vomiting (throwing up)
- Dizziness (feeling like you are spinning)
- Headache
- Trouble sleeping
- Runny tummy (diarrhoea)
- Sore joints or swollen joints
- Tendon pain or swelling
- Sore muscles
- Seeing or hearing things that are not really there (hallucinations)

When we take blood, it will not be more than a teaspoon full. We will put some cream on your skin so that the needle does not hurt too much when we take blood.

19. Can good things happen to me if I am part of this study?

People may have good things happen to them because they are in a study. These things are called “benefits.” You yourself may not benefit from being part of this study but, the new information we will get from the TB-CHAMP study will help to find out the best way to protect children against getting TB in the future. We also hope that the medical treatment and care you have in this study will help you and your family.

20. Do I have to be part of this study?

No, you do not have to be part of this study. You can also go to the government TB clinic in your local community for care. You can refuse to be part of this study. You can also tell us any time if you do not want to be part of this study any more even if you said you wanted to be part of it at the beginning.

21. Will my information be kept private (confidential)?

Yes, we will keep your information like your name, your parents’ or caregiver’s name, date of birth and so on, private. This means that we will not share it with other people.

22. Who should I ask if I have any questions about the study?

If you have any questions about this study, please tell your parent to call [site contact information] on telephone number _____

If you have questions about your rights as a person who is in this study or about things that may have hurt you because you were in this study, please tell your parent to contact [chairperson of local ethics committee] on telephone number _____

Please sign your name and surname on the next page if you agree to be part of this study.

TB-CHAMP SIGNATURE PAGE CHILD ASSENT

Signing below shows that you have been told about this study and that agree to be part of this study.

Please tick off each of the boxes below if you agree.

I agree that I have read/ been read this assent form (<i>insert version no and date</i>) for the TB-CHAMP study and that I understand what is needed of me.	
The study has been explained to me.	
I have been able to ask questions.	
My questions have been answered.	
I understand that I can choose for myself if I want to or don't want to be part of this study.	
I agree to take part in the TB-CHAMP study	

Please sign your name below.

_____ Participant's Name (print)	_____ Participant's date of birth (dd/mm/yyyy)	_____ Participant's signature
_____ Parent/ Legal Guardian (print) (As appropriate)	_____ Parent/Legal Guardian's Signature	_____ Date (dd/mm/yyyy)
_____ Staff Conducting Consent Discussion (print)	_____ Study Staff's Signature	_____ Date (dd/mm/yyyy)
_____ Witness' Name (print) (As appropriate)	_____ Witness' Signature	_____ Date (dd/mm/yyyy)

**Witness is impartial and was present for the entire consent process.*

Retain original Informed Consent Form on file. Offer participant a copy. Place a copy in medical records if applicable.

APPENDIX 6. PARENT/LEGAL GUARDIAN INFORMATION LEAFLET

Note: this information sheet provides additional information about the TB CHAMP study. This short document does not replace the detailed informed consent document for child or adolescent participation

What is this study about?

This study wants to find out whether the medicine (antibiotic) levofloxacin, can keep multidrug-resistant tuberculosis (MDR-TB) disease away in young children and adolescents who have close contact with someone with MDR-TB. MDR-TB is a type of TB that does not respond to treatment with the routine regular medicines used to treat TB. In summary, this study aims to find out whether levofloxacin can prevent MDR-TB in young children.

Levofloxacin is a routine TB medicine that is used to treat MDR-TB in children and adults in many countries in the world, also in South Africa. Young children who are below 5 years of age and who live with, or have lots of contact with, adults with MDR-TB, have a high risk of getting TB themselves. Levofloxacin has not yet been well studied to prevent MDR-TB, only to treat MDR-TB disease. The World Health Organization has specifically recommended that rigorous research be done to specifically study how to best prevent MDR-TB in children.

Why is this study important?

People who have shared a home with a person who has MDR-TB may be infected with the TB germ (that means, the TB germ is in the body). People who are infected with the TB germ often stay well, but the TB germ may start to multiply and attack the body and make people sick (they get TB disease). People who are well but are infected with the TB germ can be treated to stop the TB germ from making them sick. A normal TB germ can be killed with the usual medicines used to treat susceptible TB. However, a TB germ that does not respond to the usual treatment (MDR-TB) could possibly be treated with levofloxacin. At the moment, we do not know what the best treatment is to give to children who have been exposed to MDR-TB. This is why we are doing this study. Our study will try to answer this question in South Africa, where there is a high burden of MDR-TB.

What will happen if my child or adolescent participates in the study?

Before starting the study ("study entry")

If permission is given by the adult with MDR-TB, someone from the study team will visit your household. If you agree for your child or adolescent to take part in the study, we will see him or her at the study site.

All children and all adults in the household will be asked about symptoms of TB. If anyone in the household has symptoms of TB, they will be given a letter to take to the clinic, so they can be checked for TB.

Screening/ Entry Visit

The doctor will do some routine checks to ensure your child does not have TB disease and make sure it is safe for your child to take part in the study. These tests include taking a medical history, physical examination, X-rays of the lungs, stool samples and blood tests. There is more detailed information about all of these tests in the informed consent document.

HIV testing

As part of the study, all children are tested for HIV. This is based on national South African guidelines which recommend HIV testing in all people investigated for TB. Counselling before and after the HIV test will be provided by the study team. The HIV counselling will be provided in your preferred language. The study team will test your child at the beginning of the study and also at the week 48 visit. The results of these tests are ready within a week. The nurse or doctor will discuss these results with you.

If the HIV test is negative: Your counsellor will tell you how to keep your child from getting HIV in the future.

If the HIV test is positive: Your doctor or health care worker can take better care of your child by knowing your test result. You can learn about ways to keep your child healthy and start medicines that control HIV (antiretroviral medicine or ARVs). Your child will have access to treatment early and your doctor can start your child on ARVs to prevent your child from getting sick. If the HIV test result taken at week 48 is still the same as the first HIV test result done at the beginning of the study, we will inform you telephonically. If the result is different to previous result, we will make an appointment to discuss the results with you.

What will happen next?

If the results show that your child or adolescent is well and does not have TB disease (is not sick with TB) the following things will happen:

The child or adolescent will be enrolled on the study. We will give your child study medicine to take for 6 months. There are two types of medicine for the study. The active medicine, levofloxacin, or the placebo (inactive) medicine.

Who decides whether my child gets the active medicine or the placebo?

A computer will decide whether your child gets the active medicine or the inactive medicine (placebo). We call this computer process *randomization*. You cannot choose which medicine your child gets and the study staff also cannot choose. We do not want you or the study researchers to know which medicine your child is using, because we want to know if the “active” medicine works to protect your child from getting TB. The study team will also not know which medicine your child is on. By not knowing, we treat all children exactly the same way. We will give you medicine for your child to take every day for 6 months. At the end of the study, we will “unblind” the study and then we will know which children received which medicine. The team can then compare the two medicines.

What happens during the study and at follow-up visits

You should bring your child to the study clinic once every month for 6 months to be checked and to get more medicine. The study team will help you so that you do not run out of medicine. We know that it can be difficult giving medicines to your child every day. We want to know how well your child is taking the medicine and if there are any problems. You will be asked to fill in a treatment card and the study team will count any medicine you bring back. The study team will ask you about your experience in giving the medicine to your child. These visits can take up to 4 hours, depending on how well your child is.

After 6 months your child will stop taking the study medicine. Your child will still come to the clinic every 3 months for a further 12 months to see the study team. These follow-up visits can take up to 2 hours.

We will give you some money to pay for transport for you and your child to get to the clinic and back home for every study visit.

If at any time you think that your child may have TB disease, you must please bring the child to the study site as soon as possible. We may ask your child to produce sputum by coughing in a cup or from a gastric aspirate. A gastric aspirate involves putting a thin tube through your child's nose and aspirating (drawing up) sputum from the stomach. This is a routine procedure to test for TB in young children.

Taking the medicine

It is very important that your child takes the medicine regularly and does not miss any doses. The study medicine should not be shared with anyone else, even if you have more than one child on the study. Each child must use his/her own medicine. If the child does not take the medicine regularly it may not work properly.

What are the possible risks or side effects?

The risk of using the "real" medicine is that your child may develop side effects to the medicine. This can also happen with the the inactive medicine (placebo) In general, however, children who take levofloxacin for TB treatment tolerate it well and we rarely see side effects. We will update you on any new side effects that we see in this study and other ongoing studies, if those side effects appear to have been caused by the study medicine. More than 440 children have been already included on this TB CHAMP trial and we have not seen any concerning side effects. An independent group of people also look at the results of the study and check whether there is any problem with safety. No problems have happened yet.

The risk of using the placebo or inactive medicine, is that your child will not get medicine that may prevent the child from developing MDR-TB. Please understand that this medicine, levofloxacin, has not yet been shown to prevent children from getting MDR-TB. All children using both medicines will be followed up very carefully for signs and symptoms of TB. If your child does develop TB, it should be detected very early and your child should do well on MDR-TB treatment. All children will get very good quality of health care and will be seen by the study team at every visit.

Please tell the study team as soon as possible if you are concerned about any side effects. It may be necessary to stop the medicine until the problem goes away, or when the doctor thinks that is safe to restart the medicine. Please also tell the study team as soon as possible about any symptoms (such as cough, fever, fatigue, vomiting, loss of weight) your child develops that may be caused by TB.

Future storage of samples

At some of the visits will want to collect some extra blood (half a teaspoon, about 2.5 ml). This blood will be stored in a laboratory so that tests can be done later for research purposes for new tests, for example to look at the body's response to the TB germ. This means that we cannot give you the results of these tests since the testing will only be done later. We may also store samples of your child's sputum if the TB germ grew, and stool for future testing. New tests are being developed all the time, so we are asking your permission to use your child's samples in future for tests that are relevant to TB treatment and diagnosis.

For example, blood tests may look at how your child's genes determine whether they may develop TB, or if they are at higher risk of getting TB and how to diagnose TB. Genes are found

in every cell in the human body. Genes contain DNA which is like the 'letters' which make up the instructions or orders which the body uses to do things. The DNA in our genes influence what we look like (for example the colour of our eyes, hair and how tall we are), and sometimes the way in which our body acts when it comes across germs such as TB.

Some genes determine how well our body fights TB. Experts believe that some people have genes that may not be so good at fighting TB; which could be a reason why some people get TB and others do not, even if they live in the same place and have the same exposure to TB.

Genes or genetic material (DNA or RNA) are usually obtained from a small blood sample with your permission. At the moment we cannot say exactly what test will be done, but we give assurance that no research will be done on your child's stored samples without approval of Stellenbosch University and Wits the Human Research Ethics Committees. The samples taken from your child will never be identified by his or her name and only approved personnel working on the study would have access to them. You may withdraw consent for us to use your child's samples at any time. The samples will all be stored in South African and will be analysed in South Africa, led by investigators at Stellenbosch University.

What happens if I want my child to leave the study before it is finished?

If you want your child to leave the study early, you will be asked to bring your child in to be checked at the study site. However, you are under no obligation to have your child evaluated. This means that you can say no to bringing back your child. You may later change your mind and decide for your child to continue the follow up visits later in the study. You are welcome to do this as well. Once your child exits (leaves) the study, they will no longer be able to receive study medicine.

What if something goes wrong?

If you have any concerns about the way you or your child has been approached or treated during the study or you wish to complain, please talk to the study nurses or doctors. The Stellenbosch University and Wits University Ethics Committees oversee the conduct of this study. This study done according to the South African Good Clinical Practice Guidelines and the South African Health Products Authority (SAHPRA). Contact details for these organisations are provided for you in the informed consent form. You will also find phone number for the study team if you ever have any concerns, 24 hours a day, in the consent form.

APPENDIX 7. TUBERCULOSIS DISEASE END POINTS

Table 1. Updated international 2015 consensus definitions for TB disease end points including clinical and radiological/laboratory criteria required to make a diagnosis of confirmed, probable or possible TB in child TB contacts < 5 years of age

Case Definition	Refined Criteria ^a
Confirmed tuberculosis	Bacteriological confirmation obtained Requires <i>Mycobacterium tuberculosis</i> to be confirmed (culture or Xpert MTB/RIF assay) from at least 1 respiratory specimen
Unconfirmed tuberculosis	Bacteriological confirmation NOT obtained AND at least 2 of the following: • Symptoms/signs suggestive of tuberculosis (as defined) • Chest radiograph consistent with tuberculosis • Close tuberculosis exposure or immunologic evidence of <i>M. tuberculosis</i> infection • Positive response to tuberculosis treatment (requires documented positive clinical response on tuberculosis treatment—no time duration specified) - With <i>M. tuberculosis</i> infection • Immunological evidence of <i>M. tuberculosis</i> infection (TST and/or IGRA positive) - Without <i>M. tuberculosis</i> infection • No immunological evidence of <i>M. tuberculosis</i> infection
Unlikely tuberculosis	Bacteriological confirmation NOT obtained AND Criteria for “unconfirmed tuberculosis” NOT met - With <i>M. tuberculosis</i> infection • Immunological evidence of <i>M. tuberculosis</i> infection (TST and/or IGRA positive) - Without <i>M. tuberculosis</i> infection • No immunological evidence of <i>M. tuberculosis</i> infection

Abbreviations: IGRA, interferon-γ release assay; TST, tuberculin skin test.

^a All children should have symptoms compatible with tuberculosis as determined by the treating clinician.

Table 2. CXR features characteristic (“typical or highly suggestive CXR findings” of TB in children < 5 years of age, by disease severity status)

Non-severe disease	Severe disease
Uncomplicated LN disease (Hilar or mediastinal nodes, nodes with unilateral airway narrowing, nodes with single lobe bronchopneumonia, nodes with segmental opacification (<1 lobe)	Complicated LN disease (Airway compression with hyperinflation or collapse or bilateral airway compression)
Isolated Ghon focus	Expansile pneumonia (involving ≥1 lobe)
Simple pleural effusion	Ghon focus with cavitation
	Miliary TB
	Complicated Pleural effusion (alveolar disease with effusion, pneumothorax, loculated pyopneumothorax with air-fluid level), loculated pleural effusion
	Adult-type cavitory disease
	Bronchopneumonic consolidation with or without cavities or visible lymph nodes
	Suspected pericardial effusion (cardiac enlargement)

Conclusions of CXR review will be reported as: Highly suggestive of TB, Uncertain TB, or Not TB (refer to CXR reading forms).

The extent of lung parenchymal involvement will be classified as less than the RUL, equal to the RUL, more than the RUL, or N/A.

Table 3. Atypical CXR findings which should be recorded and considered when assessing TB disease status, include the following:

1. Normal CXR 2. Perihilar infiltrates 3. Isolated bronchopneumonia (no enlarged lymph nodes) 4. Isolated segmental opacification (no enlarged lymph nodes) 5. Calcifications 6. Generalized hyperinflation 7. Interstitial pneumonia 8. Lobar pneumonia 9. Lymphoid interstitial pneumonitis (LIP) 10. Bronchiectasis 11. Other
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Table 4. Standard classification of TB meningitis in adults and children

○ Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy. ○ Tuberculous meningitis classification ○ <i>Definite tuberculous meningitis</i> ○ • Patients should fulfil criterion A or B: ▪ A) ▪ Clinical entry criteria plus one or more of the following: acid-fast bacilli seen in the CSF; <i>Mycobacterium tuberculosis</i> cultured from the CSF; or a CSF positive commercial nucleic acid amplification test. • B) ▪ Acid-fast bacilli seen in the context of histological changes consistent with tuberculosis in the brain or spinal cord with suggestive symptoms or signs and CSF changes, or visible meningitis (on autopsy). ○ <i>Probable tuberculous meningitis</i> ○ • Clinical entry criteria plus a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or cerebral imaging criteria. ○ <i>Possible tuberculous meningitis</i> ○ • Clinical entry criteria plus a total diagnostic score of 6–9 points (when cerebral imaging is not available) or 6–11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses. Possible tuberculosis cannot be diagnosed or excluded without doing a lumbar puncture or cerebral imaging. ○ Not tuberculous meningitis ○ • Alternative diagnosis established, without a definitive diagnosis of tuberculous meningitis or other convincing signs of dual disease. ○ CSF=cerebrospinal fluid.

Appendix 8. Management of toxicities

In general, potential drug toxicity will be evaluated as described in the schedule of evaluations.

If study drug is held for toxicity, participants will have 28 weeks from enrolment to complete the 24 weeks of treatment.

Grades 1 and 2 toxicity: Participants may continue study drug, at the discretion of the site investigator, with careful follow-up.

Grades 3 and 4: Study drugs should be held until: a) return to baseline (entry visit levels) if baseline was > Grade 2, or b) until ≤Grade 2 if baseline was ≤Grade 2. Study drug may be permanently discontinued at the discretion of site investigator.

Gastrointestinal

For nausea/vomiting and/or diarrhoea ≥Grade 3, study drug should be held until the symptoms have resolved. New onset vomiting or abdominal pain (that is, patient did not vomit before or have abdominal pain and then starts to vomit or have abdominal pain with drugs) consider hepatotoxicity or hepatitis.

If nausea and vomiting occurs as a result of hepatitis that is not due to study drugs, every effort should be made to restart the study drugs after the symptoms or elevated laboratory tests subside to baseline levels.

Pseudomembranous colitis can happen with many antibiotics, including LFX, but is rare in children. Symptoms may include watery diarrhoea, persistent diarrhoea or bloody stools, stomach cramps and fever. Pseudomembranous colitis can occur even 2 or more months after antibiotic use.

For participants who develop diarrhoea or signs or symptoms concerning for colitis, consider evaluation for *C. difficile* colitis as part of the standard diarrhoea diagnostic workup. Reintroduce study drug with caution.

Antiemetic and antidiarrhoeal medication are not recommended for use in children with diarrhoea.

AST and ALT Elevation

LFX can cause elevations in ALT and AST. Concomitant illnesses, including HIV infection and hepatitis A, and other medications, including ARVs or co-trimoxazole, and paradoxical reactions, may also lead to elevated ALT and AST. Therefore, changes in AST or ALT should be evaluated within the clinical context. ALT and AST will be checked as per the schedule of evaluations for all study participants. All participants who have ≥Grade 2 elevation of AST or ALT will be evaluated for viral hepatitis (hepatitis A, B and C virus) as well as other causes of hepatitis as appropriate.

If AST, ALT, or total bilirubin increase two grades over baseline (if baseline is <Grade 2) to maximum of Grade 3, the study drugs should be held until the levels return to baseline or Grade 2. Reintroduce study drug with caution.

If baseline was Grade 2 and liver-associated enzyme(s) increase to Grade 3, no action is required.

Grade 4 is a major toxicity, and study drug should be interrupted pending resolution of the toxicity. All medications may be restarted after consultation with study team if the laboratory abnormalities were thought secondary to a concomitant illness and it is felt safe to do so. Permanent discontinuation of study drugs is at the site investigator's discretion but should be made in consultation with the protocol team.

If there is transaminase elevation of $\geq 3 \times \text{ULN}$ and elevation of total bilirubin $> 2 \times \text{ULN}$ and no other reason can be found to explain this combination, this will be treated as Grade 4 (i.e., Hy's law) [<http://www.fda/ucm076783.pdf>.]

Participants who discontinue study medications for toxicity will continue to be followed on study, off study drug.

Elevated Total Bilirubin

LFX can cause elevation in serum bilirubin level. Concomitant illnesses, including HIV, as well as other medications, including ARVs, may also increase bilirubin levels. Therefore, changes in total bilirubin should be evaluated within the clinical context.

Participants with a normal or Grade 1 total bilirubin at entry who develop isolated asymptomatic or symptomatic Grade 3 elevation of total bilirubin should have their study medications held for up to 14 days until levels and symptoms are Grade ≤ 2 , at which time therapy may be reintroduced at the discretion of the site investigator. If there is Grade ≥ 2 elevation of total bilirubin with transaminase elevation of Grade ≥ 3 , this should be treated as Grade 4 (Hy's Law). If Grade 3 toxicity develops after re-introduction of the study medications or if the Grade 3 toxicity does not resolve within 14 days, then the participant will be discontinued from study medications. The participant will continue to be followed on study, off study drugs. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness and it is felt safe to do so.

Participants who develop Grade 4 elevations of the total bilirubin will be discontinued from study medications, unless a clear alternative cause is identified. The participant will continue to be followed on study, off study drugs.

Arthritis/Arthralgia/Tendinopathy

Arthritis, arthralgia and tendinopathy are symptoms occasionally experienced by patients on LFX, although reports in young children are rare. While studies involving high doses of quinolones in juvenile animals have been shown to be associated with arthropathy and osteochondrosis, several paediatric and other human studies have not found this to be a significant concern.

If a participant develops Grade 1, 2 arthritis or arthralgia during the course of the study, he or she will continue on study drugs and be treated symptomatically according to local standards. If a participant develops Grade 3 or Grade 4 arthritis or arthralgia, the levofloxacin will be discontinued for up to 14 days until they are at Grade ≤ 2 . If participant does not reach Grade ≤ 2 within 14 days or if Grade 3 or 4 arthritis or arthralgia occurs after reintroduction of levofloxacin, levofloxacin should be permanently discontinued. Further investigations may be conducted at the site's discretion. NSAID and other symptomatic treatment will be prescribed at the discretion of the site investigator.

Following the alert from the UK Medicines and Healthcare products Regulatory Agency (MHRA) in March 2019 (Ref: <https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-new-restrictions-and-precautions-for-use-due-to-very-rare-reports-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects>), levofloxacin should be discontinued at the first sign of tendon pain or inflammation.

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The participant will continue to be followed on study, off study drug. NSAID and other symptomatic treatment will be prescribed at the discretion of the site investigator.

QTc Prolongation

Participants in this trial will be receiving a fluoroquinolone, LFX, a class of drug that has the potential to prolong the QTc interval; however LFX is less likely to cause this than moxifloxacin. ECGs will be performed only as clinically indicated as there is no evidence that either adults or children have any clinically meaningful prolongation of QTc. Clinical symptoms may include tachycardia, fatigue or palpitations. All QTc measurements will be corrected with the Fridericia correction.

For any >grade 2 QTc prolongation or signs or symptoms concerning for arrhythmia, contact the study team. Consider LFX discontinuation for up to 14 days until they are at Grade ≤ 2 . If the participant does not reach Grade ≤ 2 within 14 days or if Grade 3 or 4 QTc prolongation occurs after reintroduction of LFX, LFX should be permanently discontinued.

If a participant develops Grade 4 QTc prolongation, he or she will be hospitalized as needed and discontinued from LFX. If the prolongation is felt to be caused by a concomitant medication and resolves with discontinuation of that agent, levofloxacin may be restarted, only in consultation with the protocol team. If the team recommends permanent discontinuation of LFX, the participant will continue to be followed on study, off study drugs.

Severe Rash/Cutaneous Reaction

If Grade 3 or showing a significant increase over baseline, study drug should be held until the toxicity resolves. Study drug should be reintroduced with caution. Grade 4 cutaneous or Grade 4 mucocutaneous rashes are a major toxicity, and all study drugs should be held pending resolution of the toxicity. Study drugs may be permanently discontinued if believed to be the cause of toxicity. Study drugs may also be interrupted and reintroduced at the discretion of the site investigator.

Peripheral Neuropathy

Peripheral neuropathy has been reported in patients on LFX. Stavudine (d4T) has also been associated with the development of peripheral neuropathy.

If peripheral neuropathy develops, every effort should be made to determine the aetiology (i.e., whether the neuropathy is due to study drugs or other factors). Participants with peripheral neuropathy should be monitored carefully for any progression of peripheral neuropathy. Vitamin B 6 should be given (50-100 mg).

For Grade 1 or 2, continue the study drug and follow the participant more frequently for progression of peripheral neuropathy. Consider vitamin B6 dose.

For Grade 3 or 4, discontinue study drug until toxicity resolves to Grade ≤ 2 ; then study drug may be restarted at the site investigator's discretion. If peripheral neuropathy does not resolve despite discontinuation of study drug, the study drug will be permanently discontinued.

Central nervous system effects

Seizures have been reported in people who take fluoroquinolones including LFX. Children with a history of epilepsy or CNS disorders should therefore be carefully evaluated. Children with myasthenia gravis or Gillian Barre should be excluded from the trial. In rare instances, LFX may also cause raised intracranial pressure. The following potential adverse effects, or other changes in mood or behaviour should be reported. Further investigation should be completed as clinically indicated. Ensure that the drug dosing is correct.

- seizures
- hallucinations
- feeling restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- nightmares
- feeling lightheaded
- blurred vision
- headache

For CNS effects of Grade 1 or 2, continue at the site investigator's discretion. For grades 3 or 4, interrupt study drug temporarily for up to 14 days and restart. If the AE returns, discontinue drug permanently. In general, the dose could be reduced, and study drug re-introduced once alternative causes have been excluded. Consider ophthalmological and neurological evaluation as a priority for headache or blurred vision or new onset vomiting.

Drug-Associated Fever

If $\geq$ Grade 3, all study drugs should be held until the temperature returns to normal. Study drugs should be reintroduced with caution. Recurrence of symptoms on reintroduction will

result in permanent discontinuation of the responsible agent. No alteration of dose will occur.

Reporting

The following incidents will be systematically reported:

- Breaches of confidentiality following a TB or HIV diagnosis
- Needle stick injuries
- Grade 3 and Grade 4 adverse events
- All deaths (due to any cause) during the follow-up of child contact.