

**CAP 011**

**IMPROVING RETREATMENT SUCCESS**

**(IMPRESS): An open label randomized controlled clinical trial comparing a 24 week oral regimen containing Moxifloxacin with a 24 week standard tuberculosis (TB) drug regimen for the treatment of smear-positive pulmonary TB in patients previously treated for TB**

A research protocol prepared by:

Centre for the AIDS Programme of Research in South Africa  
CAPRISA

Funded by: European and Developing Countries Clinical Trials Partnership (EDCTP)

Principal Investigator/Project Coordinator  
Dr Nesri Padayatchi  
Principal Investigator  
CAPRISA – Doris Duke Medical Research Institute (2<sup>nd</sup> Floor)  
Nelson R. Mandela School of Medicine  
University of KwaZulu Natal  
719 Umbilo Road  
Congella  
4013, Durban

## CONTENTS

Acronyms .....	10
SCHEMA .....	11
1.0 Introduction .....	12
1.1 Background .....	12
1.2 Streptomycin .....	12
1.3 Rationale for Moxifloxacin .....	13
1.4 Lipoarabinomannan.....	14
1.5. Pharmacokinetic Study: .....	14
1.6. Use of Computerized dispensing and cellphone technology: innovative tools to enhance patient adherence, tracking and retention .....	16
1.7 SHIP Project .....	16
2.0 Study AIMS and Objectives.....	17
2.1 Primary objective .....	17
2.2 Secondary Objectives.....	17
2.3 Ancillary Objectives.....	17
3.0 Study Design and Setting .....	18
3.1 Study setting: study site and populations .....	18
4.0 inclusion and exclusion criteria.....	19
4.1 Inclusion.....	19
4.2 Exclusion.....	19
5.0 Randomization Procedures.....	20
6.0 Study Treatment.....	20
6.1 Regimens, Administration and Duration.....	20
6.2 Study product adverse effect information .....	21
6.3 Pharmacy: Product Supply, Distribution, Accountability and Storage.....	22
6.4 Adherence to study product .....	23
6.5 Antiretroviral treatment and PCP prophylaxis.....	23
6.6 Procedure for Urine LAM testing: .....	23
7. Clinical and Laboratory Evaluations .....	24
7.1 Schedule of Events (SoE).....	24
7.2 Timing of Evaluations.....	26
7.2.1 Screening Evaluations .....	26
7.2.2 Baseline, Randomization and On Study Evaluations .....	26
7.2.3 Post Entry Evaluations .....	26
7.2.4 Study Visit Window and Unscheduled Visits .....	27
7.3 Instructions for Evaluations .....	28
7.3.1 Sputum smear, culture and susceptibility.....	28
7.3.2 Specimen Storage.....	28

7.3.3 Complete Physical Exam.....	28
7.3.4 Targeted Physical Exam.....	28
7.3.5 Pregnancy Testing .....	28
7.3.6 PK sample collection.....	28
7.3.7 Urine samples for testing and storage will be drawn at the following time points in the visit schedule:.....	29
7.3.8 Procedures for computerized dispensing and cellphone technology: innovative tools to enhance patient adherence, tracking and retention:.....	29
8.0 Clinical Management Issues .....	29
8.1 Clinical Management Issues .....	29
8.2 Specific Clinical Management Scenarios.....	30
8.2.1 Missed TB doses .....	30
8.2.2 Positive smear at M4, M6.....	30
8.2.3 MDR TB.....	30
8.2.4 Withdrawal of study drug.....	30
8.2.5 Reporting AE's.....	30
8.3 Guiding Principles of Adverse Event Management.....	30
8.3.1 Grade 1 Adverse Events .....	30
8.3.2 Grade 2 Adverse Events .....	31
8.3.3 Grade 3 and 4 Adverse Events .....	31
8.4 Reporting Serious Adverse Events (SAEs).....	31
8.5 Safety Monitoring .....	31
9.0 Statistical Considerations .....	33
9.1 Sample size determination: .....	33
9.2 Analysis including statistical methods .....	34
9.3 Explanation on how the results of this study will be used .....	34
10.0 Human Participants .....	34
10.1 Patient Recruitment.....	34
10.2 Ethics.....	35
10.3 Regulatory and ethical review.....	35
10.4 Informed consent process.....	35
10.5 Participant Confidentiality .....	35
10.6 Good Clinical Practice .....	36
11.0 Data Management .....	36
11.1 Data Collection and Methods.....	36
11.2 Information management and analysis software.....	36
11.3 Data entry, editing and management, including handling of data collection forms, different versions of data.....	36
11.4 Data Storage .....	37

11.5	Quality control/assurance.....	37
12.0	Biohazard Containment.....	38
13.0	References .....	39
	Appendix I: IMPRESS Patient Informed Consent .....	42

Sites and laboratories participating in the study

<b>Clinical Research Site</b>	<b>Contact person</b>	<b>Contact Details</b>
The CAPRISA eThekweni Clinical Research Site 3 Richards Road Berea Durban 4001 South Africa	Dr Kogieleum Naidoo (Project Director)	Tel : +27 31 260 4687/1922 Fax : +27 31 307 3936 E-mail : <a href="mailto:Kogie.Naidoo@caprisa.org">Kogie.Naidoo@caprisa.org</a>
<b>Laboratories</b>	<b>Contact person</b>	<b>Contact Details</b>
<b>Storage/PBMC Laboratory</b> CAPRISA Research Laboratory NPC 11 Dan Pienaar Road Amanzimtoti Durban 4013 South Africa	Ms Natasha Samsunder (Head of CAPRISA Laboratories)	Tel : +27 31 260 4454 Fax : +27 31 260 4566 E-mail : <a href="mailto:Natasha.Samsunder@caprisa.org">Natasha.Samsunder@caprisa.org</a>
<b>Safety Bloods</b> Global Clinical and Viral Laboratory 11 Dan Pienaar Road Amanzimtoti Durban 4013 South Africa	Mr Collin Pillay Clinical Trials Manager	Tel : +27 31 9040510 Fax: +27 31 9040553 E-mail : <a href="mailto:Collin.Pillay@gcvlabs.co.za">Collin.Pillay@gcvlabs.co.za</a>

PROTOCOL TEAM ROSTER

NAME	QUALIFICATIONS	ROLE IN THE PROJECT	CONTACT DETAILS
Nesri Padayatchi	MChB, MSc (Epidemiology)	Principal Investigator /Project Coordinator	CAPRISA Offices Doris Duke Medical Research Institute (2 <sup>nd</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel: +27 31 260 4574/4555 Fax:+27 31 260 4566 E-mail:Nesri.Padayatchi@caprisa.org
Kogieleum Naidoo	MChB	Project Director	CAPRISA Offices Doris Duke Medical Research Institute (2 <sup>nd</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel:+27 31 260 4687/1922 Fax: +27 31 260 4566 E-mail: Kogie.Naidoo@caprisa.org
Tanuja N. Gengiah	B.Pharm, MSc (Epi), PHD (Therapeutics and Medicines management)	Head of Pharmacy/ Study Pharmacist	CAPRISA Offices Doris Duke Medical Research Institute (2 <sup>nd</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel:+27 31 260 4262 Fax: +27 31 260 4566 E-mail: Tanuja.Gengiah@caprisa.org
Anushka Naidoo	B.Pharm , MSc (MedSci, Clin Pharm)	Co-Investigator /Study pharmacist	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001 South Africa Tel:+27 31 260 1963 Fax: +27 31 307 3936 E-mail:Anushka.Naidoo@caprisa.org

Anneke Grobler	MSc (Biostatistician) PHD (Biostatistician)	Statistician	CAPRISA Offices Doris Duke Medical Research Institute (2 <sup>nd</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel:+27 31 260 4555 Fax: +27 31 260 4566 E-mail: Anneke.Grobler@caprisa.org
Day Munatsi	BSc (Computer Science and Statistics)	Data Manager	CAPRISA Offices Doris Duke Medical Research Institute (1 <sup>st</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel: +27 31 260 4825 Fax: +27 31 260 4566 E-mail: Day.Munatsi@caprisa.org
Dhineshree Govender	MSc (Biochemistry)	Study Coordinator	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001 Tel : +27 31 260 1905 Fax : +27 31 307 3936 E-mail : Dhineshree.Govender@caprisa.org
Charlene Harichund	MSc (Microbiology)	CTU Coordinator/ Head of Quality Assurance/ CAPRISA ExternalMonitor	Doris Duke Medical Research Institute (2 <sup>nd</sup> Floor) Nelson R Mandela School of Medicine University of KwaZulu Natal 719 Umbilo Road Congella Durban 4013 South Africa Tel: +27 31 260 4304 Fax:+27 31 260 4549 E-mail: Charlene.Harichund@caprisa.org
Rochelle Nicola Adams	MBBCh	Site Research Clinician	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001

			South Africa Tel: +27 31 260 1962 Fax: +27 31 307 3936 E-mail : <a href="mailto:Rochelle.Adams@caprisa.org">Rochelle.Adams@caprisa.org</a>
Shanisa Naidoo	MBChB	Site Research Clinician	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001 South Africa Tel: +27 31 260 1962 Fax: +27 31 307 3936 E-mail : <a href="mailto:Shanisa.Naidoo@caprisa.org">Shanisa.Naidoo@caprisa.org</a>
Tilagavathy Chinappa	MBChB	Site Research Clinician	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001 South Africa Tel: +27 31 260 1962 Fax: +27 31 307 3936 E-mail : <a href="mailto:Surie.Chinappa@caprisa.org">Surie.Chinappa@caprisa.org</a>
Aveshen Govender	MBChB	Site Research Clinician	CAPRISA eThekweni Clinical Research Site 3 Richards Road Warwick Avenue Berea Durban 4001 South Africa Tel: +27 31 260 1962 Fax: +27 31 307 3936 E-mail : <a href="mailto:Aveshen.govender@caprisa.org">Aveshen.govender@caprisa.org</a>



**CAP 011**

**IMPROVING RETREATMENT SUCCESS**

**(IMPRESS): An open label randomized controlled clinical trial comparing a 24 week oral regimen containing Moxifloxacin with a 24 week standard tuberculosis (TB) drug regimen for the treatment of smear-positive pulmonary TB in patients previously treated for TB**

**INVESTIGATOR SIGNATURE FORM**

**Version 4**

**11 May 2015**

**A research protocol prepared by:  
Centre for the AIDS Programme of Research in South Africa  
CAPRISA**

**Funded by:  
European and Developing Countries Clinical Trials Partnership (EDCTP)**

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Date

## ACRONYMS

AE	Adverse Event
AFB	Acid Fast Bacilli
ALT	Alanine transaminase
AST	Aspartate transaminase
BREC	Biomedical Research Council
ICH- GCP	International Conference on Harmonisation
CrCl	Creatinine clearance
CRF	Case Report Form
EMB / E	Ethambutol
EAE	Expedited Adverse Event
EBA	Early bactericidal activity
ECG	Electrocardiogram
eCRS	eThekwini Clinical Research Site
GCP	Good Clinical Practice
INH or H	Isoniazid
IATA	International Air Transport Association
IUD	Intrauterine Device
M.TB	<i>Mycobacterium tuberculosis</i>
MCC	Medicines Control Council
MDR	Multi Drug Resistance
NTP	National TB Programme
NVP	Nevirapine
PCZCDC	Prince Cyril Zulu Communicable Disease Centre
PID	Patient Identifier
RIF or R	Rifampicin
SA GCP	South African Good Clinical Practice Guidelines
SAE	Serious Adverse Event
SANCTR	South African National Clinical Trials Register
SAS	Statistical Analysis Software
SID	Screening Identification number
SMC	Safety Monitoring Committee
SoE	Schedule of Events
SOPs	Study Operating Procedures
TB	Tuberculosis
UKZN	University of KwaZulu-Natal
ULN	Upper limit of Normal
WHO	World Health Organization
	World Health Organization Standardized Category II
WSRR	Retreatment Regimen
PZA or Z	Pyrazinamide

## SCHEMA

**Design:** This is an open label randomized controlled clinical trial comparing two regimens for treatment of smear-positive pulmonary TB, among patients previously treated for TB. The primary objective is to determine if a Moxifloxacin-containing regimen, substituting Moxifloxacin for Ethambutol, of 24 weeks duration is superior to a control regimen of 24 weeks duration in improving treatment outcomes in patients with recurrent TB.

**Duration :** Intervention Arm : Approximately 6 months treatment + 12 months post treatment follow up

Control Arm : Approximately 6 months treatment + 12 months post treatment follow up

**Sample Size:** 330

**Population :** This study will include adults 18 years and over with a previous history of TB. HIV infected and uninfected patients will be included in the study as well as patients on ARVs provided that these are not contra-indicated with any of the study drugs. Patients with *M tuberculosis* resistance to Rifampicin will be excluded at screening using Gene Xpert technology.

**Randomization:** Patients will be randomized to receive 1 of 2 TB retreatment regimens

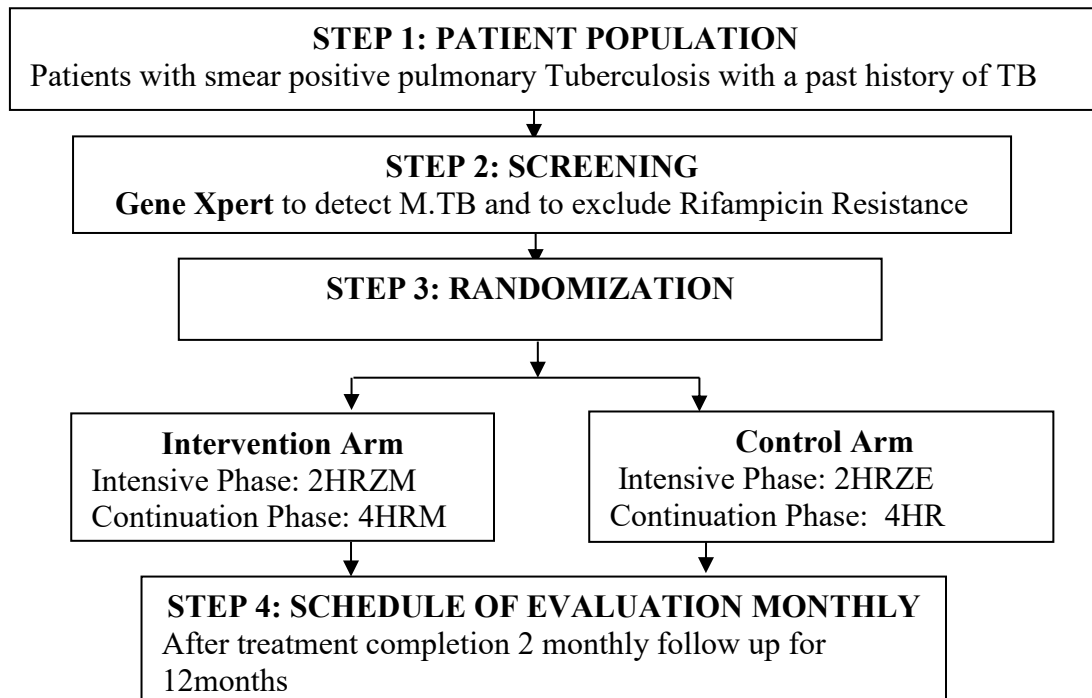


Figure 1 : IMPRESS patient screening and randomization arms

## 1.0 INTRODUCTION

### 1.1 Background

South Africa has the worst co-epidemic of tuberculosis (TB) and Human Immunodeficiency Virus (HIV) in the world where an estimated 70% of TB patients are co-infected with HIV. The dual epidemics have led to unacceptably high TB recurrence rates and previous TB treatment is a strong determinant of drug resistance<sup>1</sup>. In 2010, patients with previously treated tuberculosis comprised 15% of global TB notifications<sup>2</sup>. South Africa has the fourth highest number of multi-drug resistant TB (MDR TB) cases and the proportion of MDR TB was five times higher in those with previously treated TB<sup>3</sup>. According to the World Health Organization (WHO), an estimated 53% of retreatment TB cases were co-infected with HIV in 2011 with only 54% of these patients receiving concomitant ART<sup>2</sup>. In order to reduce the risk of recurrent TB, both the cure rate and the case detection rate need to be improved. In South Africa the treatment interruption rate on the standard WHO retreatment regimen is 12%<sup>2</sup>. This non-adherence to the retreatment regimen likely contributes to the increasing burden of MDR TB. There is a critical need for an evidence-based retreatment regimen to improve treatment outcomes of recurrent TB, a regimen that can reduce morbidity and mortality in a shorter time period. The translation of these findings to the clinical setting is urgently required as it has the potential to change current retreatment protocols which are protracted with low success rates.

The existing World Health Organization Standardized Category II Retreatment Regimen (WSRR)<sup>4</sup>, adds a single injectable drug, streptomycin, to the first line 4 drug TB treatment regimen (RHZE) in the intensive phase. This regimen, used to treat 1 million patients each year, was based on expert opinion<sup>5</sup>, and has yet to be tested in a randomized controlled clinical trial<sup>6</sup>. Previous studies of the WSRR include a systematic review, a meta-analysis and a prospective cohort study<sup>6,7</sup>. The systematic review, of published evidence of treatment of patients with a history of previous treatment or documented Isoniazid mono-resistance, included 33 trials, showed that in 1,907 patients lower failure, relapse, and drug resistance were associated with longer duration of Rifampicin, daily treatment and the use of a greater number of effective drugs.<sup>6</sup>

Streptomycin was incorporated into the WSRR, when Rifampicin was first introduced for only 8 weeks to the TB treatment regimen. Rifampicin has since been used for the full duration of standard TB treatment (at least 6 months), making the current first line TB treatment efficacious in treatment naïve patients. In addition, the WSRR was defined for settings with low prevalence of initial drug resistance; for patients treated on a regimen that included Rifampicin for only the first 2 months; and was implemented in the pre-HIV era<sup>5</sup>.

A prospective cohort study in Uganda (a high HIV prevalence setting), to assess treatment outcomes with the WSRR, demonstrated that 20% (29/148) of HIV-uninfected and 26% (37/140) of HIV-infected patients had an unsuccessful treatment outcome<sup>7</sup>. Factors associated with poor outcomes included suboptimal adherence, HIV infection, increasing age, and duration of TB symptoms. HIV infected individuals were more likely to die than HIV uninfected individuals.

There is a critical need for an evidence-based retreatment regimen that is applicable to areas with high prevalence of HIV-TB, which can shorten the duration of treatment, improve cure and completion rates, reduce morbidity, mortality and relapse rates. The proposed study aims to evaluate the efficacy of a shorter retreatment TB regimen, utilizing Moxifloxacin, a quinolone with potent activity against *Mycobacterium tuberculosis* (MTB)<sup>8</sup>.

### 1.2 Streptomycin

In recent literature there is waning support for the WHO Category II regimen<sup>6,7</sup>. In 2009, a meta-analysis and extensive systematic review (of randomized controlled trials and observational studies) was undertaken to

determine the rates of treatment failure, relapse and drug resistance in patients on the WHO retreatment regimen<sup>6</sup>. After a comprehensive search of electronic databases, the authors could find no randomized controlled trials that evaluated the effectiveness of the WHO Category II regimen. From the observational studies reviewed the authors extracted treatment failure rates and calculated that failures ranged from 18% - 44% in those with INH resistance. High rates of treatment failure on the Category II regimen have also been demonstrated elsewhere.

In 2010, the country of Georgia's National TB Programme (NTP) undertook an evaluation of treatment outcomes of patients on the WSRR regimen. The evaluation showed that there were poor outcomes among patients on the WSRR regimen and high rates of streptomycin resistance were observed among previously treated patients<sup>16</sup>. The NTP has since excluded streptomycin from the TB retreatment regimen arguing that there was a lack of evidence to support adding streptomycin to the WSRR regimen.

The category II regimen has been adopted in more than 90 countries however there is little hard evidence to support its efficacy. Instead, several authors have suggested that a new and more effect retreatment regimen is needed<sup>6,7,15</sup>.

### 1.3 Rationale for Moxifloxacin

Moxifloxacin is an 8-methoxyquinolone compound<sup>9</sup>. Several studies have demonstrated that Moxifloxacin is an effective treatment against TB and has potential to shorten the course of TB treatment<sup>8,10,11</sup>. In, 2003, a randomized controlled trial in Tanzania measured the bactericidal activity of Moxifloxacin in patients with Pulmonary TB (PTB)<sup>11</sup>. The study compared 3 groups of pulmonary TB patients. Group 1 received Isoniazid, Group 2 received Rifampicin and Group 3 received Moxifloxacin. Patients completed 5 days of monotherapy and sputum samples were collected before treatment was started and then daily for the duration of treatment. Early bactericidal activity (EBA) was measured as time taken to kill 50% of viable bacilli and the decrease in sputum viable count. The average time to bactericidal activity of Moxifloxacin was 0.88 days and the mean EBA was 0.53. For Isoniazid and Rifampicin the mean EBA was 0.77 and 0.71 respectively. The study concluded that Moxifloxacin is highly bactericidal with similar activity to Rifampicin in human patients. Gillespie *et al* (1999), tested Moxifloxacin activity against 4 other quinolones against an array of clinical isolates of mycobacteria. When compared with other quinolones; Moxifloxacin had a lower MIC against *Mycobacterium tuberculosis* than Ciprofloxacin, Levofloxacin, Sparfloxacin and Isoniazid.<sup>9</sup>

In terms of its safety profile, Moxifloxacin is well tolerated.<sup>11,12,14</sup> Two randomized controlled trials assessed the effectiveness and safety of Moxifloxacin.<sup>11,13</sup> Nausea is the most common side effect associated with Moxifloxacin however, very rarely does this result in drug discontinuation<sup>11</sup>.

In a Phase II randomized controlled trial which substituted Moxifloxacin with Ethambutol, it was determined that Moxifloxacin is well tolerated and resulted in a higher frequency of negative cultures in earlier time points among patients with smear positive pulmonary tuberculosis.<sup>11</sup> This was an important study as it demonstrated that Moxifloxacin is a suitable substitute for Ethambutol.

The principle of not adding a single drug to a failing regimen is well-known and the authors are well aware of this rule. The difference in this study is that all patients will be screened for Rifampicin susceptibility using Gene Xpert and any patient displaying Rifampicin resistance will be excluded. In addition, full susceptibility testing using MGIT, HAIN line probe assay and conventional culture will be conducted. Patients displaying multi drug resistance will be withdrawn from the study and referred for appropriate treatment at the provincial referral hospital which is within 10kms from trial site.

Moxifloxacin has been selected for use in this study due to its excellent safety profile and favourable outcomes in treating Tuberculosis. Several scientists in the field of TB research have recommended that further research on Moxifloxacin is needed to establish its ability to shorten the course of TB treatment.<sup>9,11, 14</sup>

#### 1.4 Lipoarabinomannan

Lipoarabinomannan (LAM), a glycolipid released from the cell wall of metabolically active or degrading mycobacterium, is filtered by the kidneys and excreted in urine. A new rapid, point-of-care urinary LAM antigen test, which does not require laboratory support, results in 25 minutes. This could improve the rate and speed of detecting tuberculosis (TB) in resource-limited settings. Preliminary studies have shown the rapid urine LAM test to have moderate sensitivity and high specificity for detecting culture-confirmed pulmonary TB.<sup>15</sup> In addition, the urine LAM test may perform better among HIV-infected adults with lower CD4+ T cell counts, and detects extra-pulmonary tuberculosis.<sup>15-17</sup> Additional data, including our own study, suggests that urine LAM positivity may be directly related to mycobacterial load.<sup>18,19</sup>

A point-of-care urinary LAM antigen test may have several roles. First, it may serve as an appropriate diagnostic test among TB suspects. Since the test performs well among HIV-infected patients, then the rapid test may also perform well among HIV-negative patients with a high bacillary load. If confirmed, then urine LAM testing could be expanded to HIV-uninfected patients who are active TB suspects. Second, since the test may be related to bacillary load, then one would expect LAM detection to decrease over the course of anti-tubercular therapy. If confirmed, then urine LAM testing could be used as a biomarker of response to anti-tubercular therapy.

This sub-study would be nested within the CAPRISA 011 Impress Study. All participants included in the parent study would be included in the urine LAM sub-study.

#### 1.5 Pharmacokinetic Study:

The role of therapeutic drug monitoring in anti-tuberculous therapy has gained renewed interest in the wake of an unwavering TB epidemic, the emergence of drug resistance, and suboptimal treatment outcomes in certain sub-populations of patients with TB<sup>15,16</sup>.

##### Moxifloxacin:

Moxifloxacin has been shown to be effective in the treatment of tuberculosis and may shorten time to culture conversion<sup>9,14</sup>, Moxifloxacin has few clinically relevant drug-drug interactions, although a potential drug-drug interaction exists between Rifampicin and Moxifloxacin. Moxifloxacin is not a substrate for the cytochrome P450 enzyme system, the locus of many drug-drug interactions involving Rifampicin. However, Rifampicin also induces the activity of the cytosolic enzymes glucuronosyltransferase and sulphotransferase, and Moxifloxacin is metabolized by glucuronide and sulfate conjugation. As a consequence, Rifampicin may up-regulate the metabolism of Moxifloxacin and result in decreased Moxifloxacin concentrations. One study found that concomitant Rifampicin administration results in 27% decrease in Moxifloxacin AUC.<sup>17</sup> Additional studies are needed to determine whether this difference is clinically relevant. Because Rifampicin is included in all of the treatment regimens in which Moxifloxacin is likely to be used (except those used for treatment of Rifampicin-resistant tuberculosis), it is important that the clinical relevance of this potential interaction be evaluated.

Moxifloxacin is metabolized by glucuronide and sulfate conjugation with the sulfate conjugate (M1) accounting for 38% and the glucuronide conjugate (M2) accounting for 14% of the oral dose. Another protein, P-glycoprotein, plays an important role in absorption, distribution and elimination of xenobiotics and may

affect drug concentrations of Moxifloxacin and Rifampicin containing TB drug therapy.<sup>18,19</sup> Rifampicin and the quinolones have been reported to be substrates of P-glycoprotein.<sup>20-22</sup> More than 20 single nucleotide polymorphisms have been identified in the MDR1 gene, and interethnic differences in the frequencies of MDR1 mutations leading to altered P-glycoprotein function are likely to contribute to interethnic differences in drug efficacy and toxicity. Genetic variation in the MDR1, UDP-glucuronosyl transferase and other relevant genotypes of drug metabolizing enzymes may modify Moxifloxacin and Rifampicin containing TB drug concentrations/pharmacokinetic values. Further evaluations among patients with tuberculosis disease are warranted to evaluate clinical relevance and effects on therapeutic outcomes.

The pharmacokinetic-pharmacodynamic marker that best predicts the efficacy of fluoroquinolones, including Moxifloxacin is the area under the curve (AUC) to MIC ratio.<sup>23</sup> The AUC/MIC ratio has been shown to be a reliable measure of Moxifloxacin activity. AUC/MIC ratio of > 100 has also been demonstrated to be associated with better TB treatment outcomes and greatest bacteriological activity against *Mycobacterium tuberculosis* and a decreased probability of resistance.<sup>23-27</sup>

There is very limited data on the effects of drug concentrations of the quinolones as part of first line TB drug regimens on TB treatment outcomes. Moxifloxacin has a variable pharmacokinetic profile and a number of covariates including but not limited to body mass index (BMI), co morbidities, disease severity, may affect Moxifloxacin drug concentration. This study will provide valuable information on the contribution of Moxifloxacin drug concentrations as part of a Rifampicin containing TB drug regimen on therapeutic outcomes in patients with recurrent TB.

#### Rifampicin containing TB therapy:

Since the global adoption of the Directly Observed Therapy short-course strategy, Rifampicin has remained the cornerstone of the multi-drug antimycobacterial therapy<sup>28-31</sup>. The critical role of Rifampicin in first-line therapy is well documented, and has steadily gained support due to its potent early bactericidal activity against *Mycobacterium TB* as well as its sustained activity against persistent bacilli, particularly during log-phase growth spurts<sup>32</sup>. Initial therapeutic targets for Rifampicin were guided by studies in healthy volunteers, and the subsequent dosage recommendations were based on the early high cost of the drug and fears of drug toxicity in the absence of studies on higher than recommended dose ranges<sup>16,33</sup>. Existing pharmacokinetic studies have demonstrated that current dosing practices result in Rifampicin concentrations on the lower limit of its therapeutic range, if not below it<sup>34-36</sup>. This is significant because the action of Rifampicin has been demonstrated to be concentration dependent<sup>37</sup>. Ratios of both  $C_{max}$  to MIC and AUC to MIC are important, and a  $C_{max}$  of 8 to 24 mcg/ml is recommended for optimal bactericidal activity and post-antibiotic effect<sup>16</sup>. Various factors have been demonstrated to be associated with low plasma drug concentrations which include reduced bioavailability in the context of widespread use of fixed dose combination preparations, male gender, low body weight, anaemia, hypoalbuminaemia, HIV infection, gastrointestinal disease, diabetes mellitus<sup>36</sup>. More recently, various pharmacogenetic postulates for suboptimal drug levels have emerged and will require further evaluation. A major limitation of existing pharmacokinetic data on antimycobacterial drugs is the failure to link pharmacokinetic parameters to clinical outcomes<sup>33</sup>. The few studies that have attempted to investigate the relationship between antimycobacterial drug levels and clinical outcomes all demonstrate the need to investigate current dosage practices with the view to achieving therapeutic targets<sup>15,30,33,38</sup>. The studies however, were not able to convincingly demonstrate that suboptimal drug levels were in themselves predictors of poor outcomes.

The pharmacokinetic sub-study aims to assess the relationship between Moxifloxacin and Rifampicin containing TB treatment drug levels and therapeutic outcomes and would be nested within the CAPRISA 011 Impress Study. All participants who consent to participation in this sub-study will be included.

## **1.6. Use of Computerized dispensing and cellphone technology: innovative tools to enhance patient adherence, tracking and retention**

The widespread availability of cell phone technology in resource limited settings has prompted interest in using this tool as a way to enhance adherence to medication. Cell phone networks are well developed in South Africa<sup>39</sup> and the number of cell phones in use countrywide was estimated at approximately 59,500,000 according to the GSMA Africa Mobile Observatory conducted in 2011, whereby 117.6 per 100 inhabitants in South Africa were estimated to have a cell phone. By mid-2013, total cellphone subscriptions in South Africa were estimated at over 68 million<sup>40</sup>. Thus, access to this technology is rapidly increasing. In a small qualitative study of cell phones used to report data about patient interactions, South African community-based ART counsellors described them as easy to use and without stigma<sup>41</sup>. Automated individualized text message reminders sent to 300 South African patients with TB about taking their anti-TB medications were reported to be feasible, easy, inexpensive, and resulted in a less than 2% TB treatment failure rate<sup>42</sup>.

Text messaging has been used as an intervention in various clinical trial settings and has been shown to be both cost effective and inexpensive with immediate results<sup>43,44</sup>. It is available on every type of cellular telephone, is low cost, the patient does not require special skills, training or expertise to receive, understand and interpret a text message, and it is advantageous as the patient can access the message at a later time even if the phone is switched off when the message was sent. Text messaging may also show potential as a tool for behaviour modification in disease prevention and management by virtue of the ability to provide customized, individually tailored health related communication. Timed sms'es have been shown to improve self-reported adherence from a baseline of 79% to 94%, as well as virological outcomes in HIV-1-infected patients, where baseline rate of 42% of undetectable HIV RNA viral load had increased to > 70 % at month 3, 6 and 9<sup>45</sup>. In a randomised control trial conducted in Kenya, it was demonstrated that the receipt of a sms did not directly result in any adverse effects (e.g. injury, breach of confidentiality, etc.) for the recipients<sup>46</sup>. The use of cellular phone technology is also being widely investigated in patients who cannot utilize Directly Observed Treatment, Short course (DOTS) or were not successfully treated under DOTS therapy, in order to promote drug compliance during tuberculosis treatment<sup>47</sup>.

The computerized dispensing system, iDART, has the potential to be linked to cellular phone technology that will enable a broader scope of functionality in a clinical trial setting<sup>48</sup>. This technology, known as Communicate, is an iDART compatible software package that uses cellphone functions to provide communication and information services amongst caregivers and patients in the form of sms, news alerts as well as schedule reminders.

## **1.7 SHIP Project**

Tuberculosis (TB) is a major health problem globally, and especially in South Africa. More effective intervention strategies, including TB vaccines, are urgent.

The IMPRESS sample banks and datasets, or active recruitment and sample collection platforms, will be used to identify and validate correlates of risk of TB disease, recurrent TB disease and/or protection against recurrent TB induced by the novel TB vaccine candidate, ID93 + GLA-SE. Prediction of, and protection against, recurrent TB is a major focus of new studies, given the potential for improved control of multidrug-resistant TB (MDR-TB), and leverage of high TB case accrual rates to perform small, efficient proof-of-concept TB vaccine efficacy trials.

Our aim is to develop and/or validate correlates based on common biological pathways that are fundamentally important in determining protection versus susceptibility to TB to allow prediction of TB disease risk. Prospective correlates of risk will allow selective enrollment of individuals who are likely to progress to TB disease into efficacy trials of new vaccines, dramatically reducing sample size and cost. Correlates of risk will



also guide approaches to identify correlates of protection, which could be used for assessment of vaccines in early phase trials. Finally, gains in understanding biological pathways underlying host control of *M. tuberculosis* will inform rational development of new vaccines and/or immunotherapeutics.

We have assembled a multi-institutional network of investigators at four South African and two US institutions, who collectively possess the necessary skills, capability and capacity, a diverse set of candidate correlates and TB immunopathogenesis biomarkers, and thousands of banked human samples. We will have unrivalled statistical power from one of the world's largest sets of data and banked clinical specimens to scrutinize the key transition points in TB immunopathogenesis.

We propose to systematically test if candidate correlates of risk of TB or treatment success can predict key transition points in the timeline of TB pathogenesis.

## **2.0 STUDY AIMS AND OBJECTIVES**

### **2.1 Primary objective**

The primary objective is to determine if a Moxifloxacin-containing regimen, [Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Moxifloxacin (M)], substituting Moxifloxacin for Ethambutol, of 24 weeks duration is superior to a control regimen [Isoniazid (H), Rifampicin(R), Pyrazinamide (Z), Ethambutol (E)] of 24 weeks duration in improving treatment outcomes in patients with recurrent TB.

### **2.2 Secondary Objectives**

- 2.2.1 To determine the time to culture-conversion of the Moxifloxacin regimen and the Ethambutol regimen using data from 2-, 4-, 6-, and 8-week cultures
- 2.2.2 To compare the proportion of patients with any Grade 3 or 4 adverse reactions
- 2.2.3 To compare adverse events and 2-month culture conversion rates among HIV-infected patients vs. HIV-uninfected patients
- 2.2.4 To compare the rates of treatment failure and recurrence of the Intervention and Control arm.
- 2.2.5 To compare TB cure rates at month 6 and at end of TB treatment between the Intervention and Control Arm

### **2.3 Ancillary Objectives**

- 2.3.1 To determine if the LAM antigen test is an appropriate diagnostic test for TB suspects
- 2.3.2 To determine the effect of the drug concentration and pharmacokinetic/pharmacodynamic (PK/PD) parameters of Moxifloxacin and Rifampicin containing TB therapy on TB treatment outcomes (including but not limited to sputum culture conversion rates)
- 2.3.3 To determine the extent of the drug interaction between Moxifloxacin and Rifampicin containing TB treatment, and the clinical relevance of this interaction.
- 2.3.4 To determine the presence of specific polymorphisms of drug metabolizing enzymes and investigate the effect of these on Moxifloxacin and Rifampicin containing TB drug concentrations (including but not limited to polymorphisms of MDR1, SGT and UGT genotypes).
- 2.3.5 To determine the effect of Moxifloxacin and Rifampicin containing TB drug concentrations on drug resistance.
- 2.3.6 To assess the effect of relevant covariates on Moxifloxacin and Rifampicin containing TB drug concentrations

- 2.3.7 To assess acceptability and feasibility of short messaging service (sms) reminders amongst participants with recurrent tuberculosis enrolled in a clinical trial in an urban setting in Durban, South Africa
- 2.3.8 Using computerised dispensing to generate missed visit reports and other data that will be combined with cellular phone technology to assist with monitoring patient adherence, tracking and retention
- 2.3.9 Identify and validate correlates of risk of TB disease, recurrent TB disease and/or protection against recurrent TB induced by the novel TB vaccine candidate, ID93 + GLA-SE

### 3.0 STUDY DESIGN AND SETTING

This is an open label randomized controlled clinical trial comparing two regimens for treatment of smear-positive pulmonary TB, among patients previously treated for TB. Patients will be randomized to receive one of the two TB retreatment regimens as listed below. In the Intervention Arm, Moxifloxacin will be substituted for Ethambutol. “Study drugs” refer to all the drugs listed in Table 1.

**Table 1: Study Regimens**

Study Regimens		
	Intensive phase	Continuation phase
<b>Intervention Arm *</b>	HRZM daily (first 2 months )	HRM daily (4 months)
<b>Control Arm **</b>	HRZE daily (first 2 months )	HR daily (4 months )

H – Isoniazid; R – Rifampicin; Z – pyrazinamide; E – Ethambutol; M - Moxifloxacin

\* When patients become smear negative, they will be switched from the intensive phase to continuation phase with Isoniazid, Rifampicin and Moxifloxacin for 4 months

\*\*When patients become smear negative, they will be switched from the intensive phase to continuation phase with RIF and INH for 4 months.

In this study the total duration of TB therapy will be 24 weeks (6 months) for the Intervention Arm, and the Control Arm. The duration of TB treatment may increase due to a delay in the time to sputum conversion. This will result in the extension of TB treatment beyond 6 months.

### 3.1 Study setting: study site and populations

The study will be conducted at the CAPRISA eThekweni Clinical Research Site (eCRS), adjoining the largest government outpatient TB facilities, the Prince Cyril Zulu Communicable Disease Centre (PCZCDC). The PCZCDC provides free diagnosis and treatment for patients with TB in Durban. The clinic is readily accessible by public transport. Over the last 3 years, TB cases in the Durban region have increased by 38%. In 2001, 7,819 received TB care, 70% had pulmonary tuberculosis. In 2008, 4179 TB patients were managed at the clinic and of these, 2204 had smear positive TB. Approximately 35% of patients have a past history of TB. The majority (91%) of TB patients are black Africans, unemployed (53%), women (39%), 69% are HIV co-infected and the median age was 33 years (range: 5-72 years). The change in number from 2001 to 2008 is due to the decentralization of TB services. In order to make treatment even more accessible and also improve case holding. Laboratory support is available onsite.

## 4.0 INCLUSION AND EXCLUSION CRITERIA

### 4.1 Inclusion

- 4.1.1 Adults  $\geq$  18 years of age
- 4.1.2 Previous history of anti-TB chemotherapy
- 4.1.3 HIV status: HIV infected and uninfected patients are allowed in the study:
  - 4.1.3.1 All patients must agree to HIV testing to confirm HIV status.
  - 4.1.3.2 Patients already on ARVs will be allowed in the study provided that the ART regimen is not contraindicated with any of the study agents (see 4.2.1 below).
  - 4.1.3.3 HIV infected patients at any CD4 count irrespective of ART commencement and duration will be included in the study
- 4.1.4 Smear positive
- 4.1.5 Rifampicin susceptible as determined by Gene Xpert at screening. Gene Xpert will be used to determine Rifampicin resistance, hence the study team will be made aware of resistance prior to study enrolment.
- 4.1.6 Karnofsky score  $\geq$  70
- 4.1.7 Female candidates of reproductive potential must agree to use two reliable methods of contraception while on study: a barrier method of contraception (condoms or cervical cap) together with another reliable form of contraceptive (condoms with a spermicidal agent, a diaphragm or cervical cap with spermicide, an Intrauterine Device (IUD), or hormone-based contraceptive)
- 4.1.8 A negative pregnancy test
- 4.1.9 Laboratory parameters done at, or  $\leq$  14 days prior to, screening:
  - Haemoglobin level of at least 7.0 g/dL
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT) activity less than 3 times the upper limit of normal
  - Serum total bilirubin level less than 2.5 times upper limit of normal
  - Creatinine clearance (CrCl) level greater than 60 ml/min
  - Platelet count of at least  $50 \times 10^9$  cells/L
  - Serum potassium greater than 3.0 mmol/L

### 4.2 Exclusion

- 4.2.1 Patients on a Nevirapine (NVP)-containing ART regimen at screening
- 4.2.2 Pregnant or breastfeeding
- 4.2.3 Received an antibiotic active against *M. tuberculosis* in the last 14 days (e.g. fluoroquinolones, macrolides, standard anti-tuberculosis drugs).
- 4.2.4 Patients with known *M. tuberculosis* resistance to any of the study drugs at screening
- 4.2.5 History of prolonged QT syndrome or current or planned therapy with quinidine, procainamide, amiodarone, sotalol, or ziprasidone during the intensive phase of tuberculosis treatment.
- 4.2.6 Known allergies or intolerance to any of the study drugs.

NOTE: All potential participants will undergo screening evaluations to determine eligibility. The site investigator (or designate) will assess eligibility and ensure that the participant meets all of the inclusion criteria.

## 5.0 RANDOMIZATION PROCEDURES

Patients will be randomized to the two arms using permuted block randomization (e.g. blocks of variable sizes 4 or 6) stratified by HIV status. The randomization will be done by a statistician and the randomization codes will not be available to study staff until the participant is randomized. This will be done by providing sealed opaque randomization envelopes to the research staff at the CAPRISA – eThekweni CRS. The envelopes will be stored in a locked cupboard and opened in sequential order by study team members authorized to perform randomization procedures by the Principal Investigator. After opening the envelopes, staff will record the date and time of opening the envelope and their staff details. The patient’s allocated arm will then be recorded on a randomization log.

## 6.0 STUDY TREATMENT

### 6.1 Regimens, Administration and Duration

Once randomized to either the Control or Intervention arms the study drug is to be self-administered once daily before meals. Treatment should be commenced no more than 3 days after randomization. The Control and Intervention arms will follow the South African National Tuberculosis dosing guidelines for re-treatment cases as closely as possible. All patients will receive pyridoxine 50mg daily whilst in the study.

**Table 2: Study drug regimens and duration: Control arm**

Pre-treatment body weight  (kg)	Intensive phase 7 days a week for 8 weeks  (56 doses)	Continuation phase – 7 days a week for 16 weeks  (112doses)	
	RHZE (150,75,400,275 mg)	RH (150,75 mg)	RH (300,150mg)
30-37	2 tabs	2 tabs	
38-54	3 tabs	3 tabs	
55-70	4 tabs		2 tabs
>71	5 tabs		2 tabs

H – Isoniazid; R – Rifampicin; Z – pyrazinamide; E – Ethambutol

**Table 3: Study drug regimens and duration: Intervention arm**

Pre-treatment body weight	Intensive phase 7 days a week for 8 weeks <b>(56 doses)</b>				Continuation phase – 7 days a week for 16 weeks <b>(112 doses)</b>				
	(kg)	RH (150,75mg)	RH (300,150mg)	Z (500mg)	M (400mg)	RH (150,75mg)	M (400mg)	RH (300,150mg)	M (400mg)
30-37	2 tabs		2 tabs	1 tab	2 tabs	1 tab			
38-54	3 tabs		3 tabs	1 tab	3 tabs	1 tab			
>55		2 tabs	4 tabs	1 tab			2 tabs	1 tab	

H – Isoniazid; R – Rifampicin; Z – pyrazinamide, M - Moxifloxacin

In this study the total duration of TB therapy will be 24 weeks for the intervention arm, and the control arm. The duration of TB treatment may be extended depending on the time to sputum conversion.

In this study the total duration of TB therapy will be 24 weeks for the Intervention arm, and for the Control arm. The duration of TB treatment may increase due to a delay in the time to sputum conversion. This will result in the extension of TB treatment beyond 6 months. The required number of doses must be completed by the patient for the intensive phase of TB treatment before the patient can initiate the continuation phase of TB treatment. The study pharmacist and study clinician will monitor the number of doses ingested, by pill count, for each phase of treatment. The patient’s weight will be assessed monthly and the dose of the study product will be adjusted in accordance with the patient’s weight which will be assessed monthly.

In addition to the 6 months of TB treatment regimen, patients in the Intervention Arm, who provide informed consent to take part in the PK sub-study may be requested to take a single dose of Moxifloxacin 400mg, at the Month 7 visit (or subsequent visit if Month 7 visit has been missed). This PK sample for single dose moxifloxacin may be deferred to month after TB treatment completion on participants who have TB treatment extended beyond 6 months

## 6.2 Study product adverse effect information

Table 4 outlines possible adverse effects and drug interactions. However, this list is not all inclusive and each adverse effect must be examined in conjunction with the full clinical picture. At each clinic visit patients will be asked about adverse events that have occurred since their previous visit and physical examination will be performed.

**Table 4: Possible adverse effects and drug interactions.**

Study Drug	Adverse effects	Drug interactions	Comments
Rifampicin	Gastro-intestinal: nausea, anorexia, mild abdominal pain, diarrhea. Cutaneous reactions: mild flushing and pruritus. Hepatitis especially if alcoholic or history of liver disease.	Efavirenz, nevirapine, protease inhibitors. Rif is an enzyme inducer and increases metabolism of oral anticoagulants (warfarin), oral diabetic drugs, digoxin, phenobarbitone and other anti-epileptics.	Colours urine, sweat and tears orange-pink.

	Serious: flu-like syndrome and shock		
Isoniazid	Peripheral neuropathy, hepatitis (mostly in those > 35yrs), generalized skin rash, fever, joint pains – rare.	Inhibits metabolism of anti-epileptics.	
Ethambutol	Progressive loss of vision caused by retrobulbar neuritis, usually manifests first as loss of colour vision and usually presents after the client has been on treatment for at least two months. This is usually caused by excessive doses of Ethambutol. Skin rash, joint pain, peripheral neuropathy.	There are no known drug–drug interactions involving Ethambutol.	Do not administer if optic neuritis present.
Pyrazinamide	Liver damage: anorexia, mild fever, tender enlargement of the liver and spleen may be followed by jaundice. Arthralgia: This is common and mild. The pain affects both large and small joints, the level of uric acid is increased and gout may occur. Skin rash on sun exposed areas.	Low potential for drug interactions.	
Moxifloxacin	Prolonged QT interval, well tolerated – low rates of gastrointestinal adverse effects.	Potential interaction: Rifampicin, iron/iron containing supplements, aluminium/magnesium containing antacids, zinc/zinc containing supplements, didanosine, sucralfate.	

### 6.3 Pharmacy: Product Supply, Distribution, Accountability and Storage

All TB treatment with the exception of Moxifloxacin will be procured from the Department of Health and where possible fixed dose combinations of drugs will be utilized (outlined in Table 2 and 3). Moxifloxacin 400mg tablets will be procured in bulk quantities from Bayer Healthcare and will be packaged for patient use at the study pharmacy under Good Pharmacy Practice guidance.

The study pharmacy will maintain accountability records of all study products dispensed. In addition, records of manufacturer, batch number and expiry information will be maintained by the study pharmacist. Unused product will be re-issued to the participant at the discretion of the study pharmacist and in accordance with the stipulated dosing schedule.

Dispensing of study product will be done either directly to the study patient or to authorized study staff if the patient is unable to present in person to the study pharmacy.

Study product will be stored between 15- 25°C and temperature records will be maintained at the study pharmacy. Destruction of unused and never dispensed study product will be managed in accordance with the study pharmacy SOP on study product destruction after study PI approval.

#### **6.4 Adherence to study product**

Adherence to study product will be assessed at the study pharmacy at each study visit. This will be achieved by pill count reconciliation and will be documented on a case report form (CRF). Patient self-reported reasons for non-adherence will be assessed and adherence counseling will be provided if needed.

#### **6.5 Antiretroviral treatment and PCP prophylaxis**

Patients, who initiate the study whilst on antiretroviral therapy or during the course of the study require antiretroviral therapy, will be given a regimen that substitutes nevirapine with efavirenz. Patients found to be HIV infected may be given cotrimoxazole/dapsone prophylaxis in accordance with HIV/AIDS guidelines implemented locally.

#### **6.6 Procedure for Urine LAM testing:**

Urine samples will be tested for LAM antigen using the Determine™ TB LAM Ag test (Alere, Waltham, USA). First, participants will be given a urine specimen container and a private space to provide a urine sample. The site nursing staff will use a manufacturer provided pipette to transfer 2 drops (approximately 60 µL) of urine to a small area of the test card. Two people will then independently interpret each result between 25-35 minutes after starting the test. A small reference card, which will aid in correctly interpreting the result, will be available. If positive, the test result will be scored from 1+ to 5+, depending on the severity of the colorimetric line. A score of 1+ represents a weakly positive test result, and a score of 5+ represents a strongly positive test result. Once completed, the test card will be discarded and the urine sample will be placed in frozen storage along with other biologic specimens. The results of the rapid urine test will not be used for clinical treatment decision.

## 7. CLINICAL AND LABORATORY EVALUATIONS

### 7.1 Schedule of Events (SoE)

**Table 5: Study Table of Evaluations**

Procedures	Screening	Baseline	Week			Study Months														
			2	4	6	2	3	4	5	6	7	8	10	12	14-24 (*2 monthly)	End TB Treat	Recurr ence <sup>6</sup>	Termi nation	Time of IRIS	Time of Serocon version
Inclusion & Exclusion Criteria		X																		
Informed Consent	X																			
Randomization		X																		
HIV test (performed monthly for HIV negative participants)	X <sup>1</sup>		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical , Medication and TB History & Physical Exam	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals (including Pregnancy test )	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception confirmation	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X			X	X	X	X	X	X	X	X	X		X				
GeneXpert	X																			
Sputum Smear	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Culture : <b>INTERVENTION ARM:</b> until 6 months		X	X	X	X	X	X	X	X	X					X	X	X			
Culture: <b>CONTROL ARM:</b> until 6 months		X	X	X	X	X	X	X	X	X					X	X	X			
Susceptibility		X				X				X*		X*				X	X			
PAXgene for SHIP Study		X				X				X		X			X	X	X	X		
Urine (Lam Testing)		X				X			X	X						X				
Chest radiograph		X <sup>2</sup>					X			X						X	X			
ECG **		X				X		X		X										
Vision testing (Snellen and Ishihara) <b>Control Arm only</b>		X				X														



Procedures	Screening	Baseline	Week			Study Months											End TB Treatment	Recurrence	Termination	Time of IRIS	Time of Seroconversion
			2	4	6	2	3	4	5	6	7	8	10	12	14-24 (*2 monthly)						
AST, ALT, Bilirubin, Hb, platelets, & Full blood count, Creatinine clearance, potassium, total protein, alkaline phosphatase and as clinically indicated	X	X <sup>2</sup>				X		X		X							X	X	X	X	X
CD4 Count ( <b>HIV Infected patients only</b> )	X					As per SA HIV guidelines														X	
Viral Load ( <b>HIV Infected patients only</b> )	X																	X		X	
HBsAg	X																				
PK Samples (Intervention Arm)				X		X <sub>3</sub>				X	X <sup>4</sup>										
PK Samples (Control Arm)						X															
Specimen Storage		X	X		X		X						X				X				X
PBMCs***		X <sup>5</sup>				X				X					X	X	X	X	X	X	X

1: HIV Testing is required at screening for all potential participants. Thereafter, HIV testing will be required for HIV negative participants only as per SoE above.

2: A chest radiograph/Bloods will be repeated if they are more than 14 days old

3: PK blood samples, in the intervention arm only, will be taken once during the intensive phase of TB treatment at either Week 4 **OR** Month 2 (**PK bloods may be repeated at Month 2 if these were not taken, incorrectly done or incomplete at Week 4 OR at the discretion of the investigator**), and at the end of TB treatment (Month 6)

4: Additional PK samples will be taken at M7 (or the first visit after if Month 7 is missed) in Intervention Arm before and after the ingestion of the single additional dose of Moxifloxacin. This additional PK sample may be deferred to month after TB treatment completion on participants who have TB treatment extended beyond 6 months

5: If PBMCs are not collected at baseline samples may be taken at Week 4 or Month 2

6. End of TB Treatment visit will be conducted within 7 days of completion of TB treatment.

\* Samples will be collected and stored for future susceptibility testing,

\*\*ECG's will be done at baseline, Month 2 and Month 4 and Month 6. ECG's will be performed 2 monthly during treatment with Moxifloxacin

\*\*\*Additional PBMC's will be collected at IRIS and at the time of seroconversion

The study SoE will be followed except when procedures are clinically indicated as not required.

## 7.2 Timing of Evaluations

Refer to Table 5 above for a summary of the evaluations.

### 7.2.1 Screening Evaluations

#### Informed Consent

After identifying potential patients for the study, written informed consent must be obtained from these patients.

#### HIV Testing

HIV testing will be carried out using a licenced rapid HIV test. HIV positive results will be confirmed by a second licenced rapid HIV test. Discordant results will be confirmed by ELISA.

#### Clinical and Laboratory Evaluations

Patients will have height and weight measured, and blood will be drawn for an AST, ALT, total bilirubin, potassium, alkaline phosphatase, total protein Creatinine clearance, unless results from these tests within the previous 14 days are available. A pregnancy test (using urine sample) is required at every visit if patient is a woman of child-bearing potential.

A chest radiograph will also be taken, unless a chest radiograph done within the previous 14 days is available for review. A sputum sample will be obtained for smear and GeneXpert analysis to ascertain Rifampicin resistance and confirm TB infection. Screening evaluations to determine eligibility must be completed  $\leq 14$  days prior to randomization.

In addition to data being collected on participants who enrol into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the study database.

### 7.2.2 Baseline, Randomization and On Study Evaluations

Eligibility criteria will be assessed by a study clinician prior to randomization. On-study entry evaluations will occur after randomization. Entry evaluations must be completed no more than 3 days after randomization. When the results of the blood tests and chest radiograph are available, and if the patient meets the enrolment criteria, the site must then randomize each new patients according to Section 5 (Randomization Procedures) above. Note, the result of HIV testing is required for randomization. Baseline evaluations (according to SoE, Table 5) will be completed on the same day of the randomization (unless otherwise stated by the Study PI or study clinician) and patients should start on assigned study therapy as soon as possible after randomization but no more than 3 days following randomization.

### 7.2.3 Post Entry Evaluations

#### Study visits - intensive phase of therapy

Intervention Arm - study visits Week 4 and Month 2 will be considered as intensive phase

Control Arm - study visits Week 4, Month 2 will be considered as intensive phase

A delay in the time to sputum conversation may result in an extension of the intensive phase.

Regardless of arm, at each study visit for which the patient is in the treatment phase, a sputum sample will be obtained. Sputum induction will be resorted to in the event that the participant is unable to provide a

spontaneous, good quality sputum specimen. Laboratory tests for safety monitoring will also be obtained at study visits during the intensive phase of therapy. Vision testing will be performed at baseline and repeated at Month 2 for Control Arm only. Patients found to have HIV infection will have blood drawn for a CD4 cell count and HIV RNA level at the first study visit after HIV infection is confirmed (as per the study SoE). PBMC samples will be collected if a patient seroconverts whilst on study.

Follow up management of HIV-infected patients will be as per SA HIV guidelines.

#### Study visits – continuation phase of therapy

Intervention arm - study visits Month 3 to Month 6 will be considered as continuation phase.

Control arm - study visits Month 3 to Month 6 will be considered as continuation phase.

Month 4 – Patients will have an assessment for toxicity from the four-drug phase of therapy. This will consist of a symptom-driven examination, and laboratory testing (complete blood count and serum AST, total bilirubin, and serum creatinine). A sputum specimen will be obtained for culture.

Month 4-6–Patients will continue to have study visits monthly during the continuation phase of therapy. Sputum cultures will be obtained at Month 4, Month 5, Month 6 during the continuation phase of therapy. Laboratory testing, other than sputum cultures, will be at the discretion of the principal investigator/study clinician.

#### Pharmacokinetic studies

PK studies will be conducted on a subset of the study population. PK analyses will assess the potential interaction between Moxifloxacin and Rifampicin containing TB treatment in patients with recurrent TB, and to determine the effect of Moxifloxacin and Rifampicin containing TB therapy drug concentrations on TB treatment outcomes.

#### Lipoarabinomannan studies

All participants included in the parent study would be included in the urine LAM sub-study. Participants would provide urine samples at baseline, as well as 2- and 5 months into anti-tubercular therapy. One additional urine sample will be collected at the end of the assigned treatment course for each participant. Each urine sample would then be tested using one rapid urine LAM test strip in a designated laboratory. Once completed, the test card will be discarded and the urine sample will be stored in a freezer for future testing.

#### *7.2.4 Study Visit Window and Unscheduled Visits*

The window period for all scheduled monthly study visits  $\pm 7$  days. Any visit for which a patient attends outside of the specified visit window but not in addition to those required as per the ‘schedule of evaluations’ should be considered as an early/late visit. The assessments which are undertaken as part of an early/late visit should reflect those for the visit which will be or has been missed. Any additional assessments should be undertaken as clinically indicated.

## 7.3 Instructions for Evaluations

### 7.3.1 Sputum smear, culture and susceptibility

At the time points indicated in the SoE, a sputum sample will be collected for AFB smear, mycobacterial culture and susceptibility.

### 7.3.2 Specimen Storage

Specimens for storage will be stored according to timelines stated in the SoE. In addition to the scheduled timelines, samples found to be culture positive at baseline, Month 4 through Month 8 should be stored. In addition, sputum isolates from smear testing will be stored.

### 7.3.3 Complete Physical Exam

A complete physical examination will be performed at screening only and will include at a minimum Karnofsky performance score, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure), height, weight, and full examination.

### 7.3.4 Targeted Physical Exam

A targeted physical examination will be performed at every study visit from baseline and on subsequent clinically required visits

### 7.3.5 Pregnancy Testing

For women of reproductive potential: The pregnancy test performed at study according to SoE must be negative.

### 7.3.6 PK sample collection

Plasma samples for storage will be drawn at the following time points in the visit schedule:

- Week 4 (Intervention Arm) OR Month 2 (Intervention Arm)
- Month 2 (Control Arm)
- Month 6 (Intervention Arm)
- Month 7 (Intervention Arm) or one month post end of TB treatment

The duration of the intensive phase of TB treatment may increase due to a delay in the time to sputum conversion. If the duration of TB treatment is extended:

- For Month 6 PK blood draw, End of continuation phase TB treatment (Month 6- Intervention Arm) sometimes the PK is not at end of the continuation phase because TB treatment is extended.
- Month 7 PK blood will be completed at the month following the completion of TB treatment.

Participants will be counselled to take their doses of TB treatment at a similar time once daily until the day before their scheduled study visit. The TB treatment dose on the day of the PK study visit will be ingested by participant at the study clinic. Plasma samples will be taken in the study clinic prior to the dose of TB therapy (Intervention Arm) and at specified time points in the course of the study visit. The plasma will be placed on ice and sent to the CAPRISA laboratory to be centrifuged and stored at –80 degrees Celsius for analysis at a later time.

## Pharmacogenetic Studies:

Drug metabolizing enzymes will be assessed to investigate the effect of specific polymorphisms on drug concentrations/pharmacokinetics of moxifloxacin and rifampicin containing TB therapy.

7.3.7 Urine samples for testing and storage will be drawn at the following time points in the visit schedule:

- Baseline (Both Arms)
- Month 2 (Both Arms)
- Month 5 (Both Arms)
- Month 6 (Both Arms) End of TB Treatment (Both Arms)

7.3.8 Procedures for computerized dispensing and cellphone technology: innovative tools to enhance patient adherence, tracking and retention:

Participants who are enrolled and agree to receive a sms within the IMPRESS study will have their cellphone numbers entered onto the Communicate database. Different sms campaigns will be created, using the various cellular phone technology –based functions available:

- An appointment reminder to go out 3 days before the participant is scheduled to present to the clinic, or sooner if visits are scheduled frequently over a short period of time: *“Please do not forget your appointment at the clinic in three days’ time”*
- For those participants who are included in the pharmacokinetic sub-study, a broadcast sms sent out the evening before a scheduled visit, which reminds the patient not to take an evening/morning dose, prior to sample collection at the clinic for pharmacokinetic (PK) study, the next morning: *“Please do not take your TB medication the night or morning before coming to the clinic. Carry TB drugs with you to be taken at the clinic.”*
- A sms to prompt defaulters to return to the clinic: *“You have missed your appointment at the clinic. Please return to the clinic as soon as possible.”*
- An motivational broadcast sms to enhance patient compliance by re-enforcing adherence, programmed to be sent one week after enrolment, and periodically thereafter: at the end of month 1 of treatment and then at the beginning of the continuation phase: *“TB can be cured and the spread of TB stopped if the full course of treatment is taken correctly, so that people can lead fuller, safer and healthier lives.”*

## 8.0 CLINICAL MANAGEMENT ISSUES

### 8.1 Clinical Management Issues

The IMPRESS study will use the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table) Version 1.0, December 2004 (Clarification, August 2009)

- Patients need to be assessed for evidence of musculoskeletal toxicity at every study visit through history taking and physical examination.
- Ocular toxicity will be assessed using the Snellen and Ishihara tests at baseline and month 2 and/or when clinically required (Control Arm only). Patients will be educated about symptoms of ocular toxicity before treatment initiation, and will be assessed for ocular toxicity for the duration of TB therapy when Ethambutol forms part of the TB regimen. The Snellen and Ishihara tests will be repeated if any symptoms of ocular toxicity or any change in vision occurs.

- All patients will undergo ECG monitoring at baseline, Month 2, Month 4, Month 6 (and 2 monthly whilst being administered with Moxifloxacin). This will be repeated if patients complain of chest pain or syncope. Moxifloxacin will be substituted for Ethambutol if there is evidence of QT prolongation, or if patients QRS complexes change in amplitude from baseline.
- Patients must not have evidence of severe or life-threatening liver disease at baseline (Bilirubin, AST and ALT < 5 times the ULN), no evidence of renal impairment i.e. creatinine clearance of > 60 mls/min, serum potassium of > 3.0 mmol/l.

## 8.2 Specific Clinical Management Scenarios

### 8.2.1 Missed TB doses

Extend treatment to allow patient time to complete requisite doses.

### 8.2.2 Positive smear at M4, M6

Investigate for treatment failure, and change therapy if accompanied by clinical or radiologic deterioration or relapse of symptoms and follow local TB management guidelines.

### 8.2.3 MDR TB

Patients withdrawn from study because their initial TB isolate is found to be MDR –TB will not be followed up further, unless required for patient safety (e.g. an adverse event present, in which case follow-up should occur as clinically indicated).

### 8.2.4 Withdrawal of study drug

An investigator may withdraw one or all drugs in the study treatment in the event of a serious or life-threatening adverse event, if this is deemed to be in the patients' best interest. This needs to be discussed with the study PI or designee before the decision is made, unless in an emergency situation. All safety issues need to be followed up until resolution to  $\leq$  Grade 2 (DAIDS Table for Grading Adult and Paediatric Toxicity Events)

### 8.2.5 Reporting AE's

The study drugs are Moxifloxacin, Ethambutol, Isoniazid, Rifampicin, and Pyrazinamide. The most common adverse effects known to be associated with the study drugs are summarized in the protocol (see Table 4 above). The investigators are responsible for reporting all Grade 3 and Grade 4 adverse events that are observed or reported during the study, regardless of whether they are thought to be related to the study drugs in patients chart notes. All Adverse Events including SAEs will be reported in accordance with ICH and SA GCP guidelines.

## 8.3 Guiding Principles of Adverse Event Management

For adverse events, that is in the investigator's judgment may be due to study drugs, the following approach to management should be applied:

### 8.3.1 Grade 1 Adverse Events

In general, for grade 1 events the patient will be followed carefully and the study drugs will be continued.

### 8.3.2 Grade 2 Adverse Events

For grade 2 events the patient will be followed more closely, with additional laboratory and/or clinic visits as necessary; drugs should be continued unless in the view of the investigator this would be unsafe.

### 8.3.3 Grade 3 and 4 Adverse Events

Any grade 3 or 4 event should be carefully assessed. The research clinician should rule out other possible causes of the symptoms before discontinuing study medication. When possible, concomitant medications should be with-held first at the discretion of the research clinician if causality is suspected. If after careful assessment and in the clinician's judgment the event is due to study drug(s), the causative study drug(s) may be withheld. The patient should be permanently discontinued from study medications if it is in their best interests to do so. Further treatment of the TB will be directed by the clinician in consultation with the investigator. The patient will continue to be followed according to the protocol. Other adverse events of any grade not thought to be due to the study drugs, should be managed at the discretion of the research clinician; study treatment should be continued, if possible.

## 8.4 Reporting Serious Adverse Events (SAEs)

The following Serious Adverse Event will be reportable to the database and regulatory authorities: AE's that:

- Results in death
- Is immediately life threatening at the time of occurrence
- Results in persistent or significant disability or incapacity
- Requires in-patient hospitalization or prolongs hospitalization
- Results in a congenital anomaly or birth defect
- Is deemed an "important medical event" by the Investigator (may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient e.g. convulsions. This will include any adverse event that *is unexpected, but related* to the study product, e.g. asymptomatic prolonged QT interval associated with Moxifloxacin.

## 8.5 Safety Monitoring

### Procedures for assessing safety

At each clinic visit patients will be asked about changes (adverse events) that have occurred since their previous visit. Physical assessments will be performed at baseline and on subsequent scheduled visits.

Safety laboratory investigations will be performed at screening and in accordance with the schedule of evaluations, as well as determined by the study clinician based on the evaluation.

1. Screening tests and scheduled subsequent visits will include: Liver function, renal function, full blood count: At screening, baseline and every second month until Month 8 of follow up. Thereafter, tests will be performed at the end of TB treatment, time of TB recurrence and at the study termination visit.
2. 2. Pregnancy test: At screening, baseline and every month thereafter as per the SoE.

For isolated asymptomatic or symptomatic Grade 3 elevation of total bilirubin all medications should be discontinued and held for up to 14 days until levels and symptoms are Grade  $\leq 2$ , at which time therapy may be reintroduced. If there is  $\geq$  Grade 2 elevation of total bilirubin with transaminase elevation of grade  $\geq 3$ , this

should be treated as Grade 4. 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.

Participants who develop Grade 4 elevations of the total bilirubin will be discontinued from study medications. The participant will continue to be followed on study, off study drugs.

Any additional test that the investigator deems necessary for the clinical evaluation of the subject can be performed.

Any adverse events detected will be graded according to a modified version of the toxicity criteria produced by the Division of AIDS and coded using MedDRA.

### QTc Prolongation

Participants in this trial may receive Moxifloxacin which has the potential to prolong the QTc interval. All QTc measurements will be corrected with the Fridericia correction.

The protocol-specific criteria for grading prolonged QTc are as follows:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Prolonged QTc (using Fridericia QT correction formula)	Asymptomatic, QTc interval 0.45 – 0.47 sec	Asymptomatic, QTc interval > 0.47- < 0.50 sec	Asymptomatic, QTc interval $\geq$ 0.50 sec OR a QTc > 0.48 sec with an increase in interval $\geq$ 0.06 sec above baseline	Life threatening consequence, eg, Torsade de pointes or other associated serious ventricular dysrhythmia

If Grade 2 QTc prolongation develops during the course of the study and is felt to be due to study medications, the participant will be monitored more closely, with twice weekly visits and QTc evaluation. If Grade 3 QTc prolongation occurs, all study drugs will be discontinued and the participant will be referred to hospital for further assessment and management. If the QTc prolongation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

If a participant develops Grade 4 QTc prolongation, he or she will be hospitalized and discontinued from study medications. If the prolongation is felt to be caused by a concomitant medication and resolves with discontinuation of that agent, study medications may be restarted. Otherwise, the participant will be referred to the NTP for treatment of his or her TB according to local standards of care. The participant will continue to be followed on study, off study drugs.

Serious adverse events will be reported to the MCC and the UKZN Biomedical Research Ethics Committee. (BREC) according to their specific requirements.



## **Outcome status**

### *Definition of treatment failure:*

Patient whose baseline smear (or culture) was positive and remains or becomes positive again at 5 months or later during treatment. This definition excludes those patients who are diagnosed with RR-TB or MDR-TB during treatment.

### *Definition of treatment cure*

Patient whose baseline smear (or culture) was positive at the beginning of the treatment and is smear/ culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior.

## **Discontinuation of study treatment**

The investigator may discontinue a patient from treatment in the event of a severe or serious adverse event, or at any time he/she thinks it's in the patient's best interest. If there is a medical reason for withdrawing study treatment, the patient will remain under the supervision of the investigator until satisfactory health has returned irrespectively of the reason for discontinuation. The frequency of patient review will be determined by the clinical need to ensure optimal care.

## **Withdrawal from the study**

Patients withdrawn from study due to a protocol violation will be included in the safety database of the study. Patients withdrawn from study because their initial TB isolate is found to be MDR –TB will not be followed up further, unless required for patient safety (e.g. an adverse event present, in which case follow-up should occur as clinically indicated). Similarly, patients withdrawn from study because their initial cultures are negative do not need to be followed up further (unless there is an ongoing adverse event). Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time for any reason. Patients who withdraw their consent will not have to undergo any follow up procedures.

This study will be reviewed by a Safety Monitoring Committee (SMC) that meets for scheduled reviews of studies every year. A full SMC review will include an efficacy review and a futility review for detecting a survival difference. A full review will be scheduled at least annually after opening to accrual or on a frequency determined by the SMC. For each full review, summaries provided to the SMC will be broken down by treatment arm. Participants' baseline demographic and health characteristics will be summarized. Review of study conduct will address site accrual, premature study discontinuations and their reasons (administrative or loss to follow-up), tracking of potential losses to follow-up, data completeness. The SMC will also review participants' safety data, frequency and causes of death, as well as incidence of TB recurrence.

In addition, quarterly internal reviews of patient charts, SAE reports and regulatory submissions will be conducted.

## **9.0 STATISTICAL CONSIDERATIONS**

### **9.1 Sample size determination:**

A total of 330 patients will be enrolled. A two group continuity corrected chi square test with a 0.05 two-sided significance level will have 80% power to detect the difference between 75% of patients having culture conversion in the Intervention arm and 60% of patients having culture conversion in the Control arm. A previous unpublished retrospective review at the study site comparing the treatment outcome in retreatment

patients with TB using the standard 4 drug regimen, showed a cure and completion rate of 60.1%. According to WHO surveillance data, the retreatment regimen is successful in about 70% of patients, and other retrospective studies show treatment success rates of 26 – 92%. Thus, 75% is a realistic cure and completion rate to aim for in the Intervention group. A previous unpublished retrospective review at the study site comparing the treatment outcome in retreatment patients with TB using the standard 4 drug regimen, showed a cure and completion rate of 60.1%. According to WHO surveillance data, the retreatment regimen is successful in about 70% of patients, and other retrospective studies show treatment success rates of 26 – 92%. Thus, 75% is a realistic cure and completion rate to aim for in the Intervention group.

## **9.2 Analysis including statistical methods**

To answer the primary objective of this study the sputum culture conversion rates at the end of the intensive phase and at month 6 will be compared between the two treatment arms. This will be done by calculating the proportion of culture conversions in each of the two arms and comparing these using the chi-square test.

## **9.3 Explanation on how the results of this study will be used**

Many published reports have questioned the effectiveness of the standard WHO retreatment regimen and, more importantly the potential for amplification of TB drug resistance. Despite the enormous patient and public health cost of drug resistant TB, there has been a lack of research effort directed at investigating alternate regimens aimed at optimising treatment outcomes among retreatment patients who are most at risk of developing acquired drug resistant TB. This study proposes to use a regimen that omits an injectable agent, enhances time to culture conversion thereby shortening duration of treatment, increasing adherence and completion rates and reducing the likelihood of acquiring drug resistance. The availability of new generation rapid diagnostic technologies offers a unique opportunity of providing a targeted retreatment approach without compromising the efficacy of second line agents used to treat drug resistant TB. The goal of global tuberculosis research and control efforts to date has been the development of shorter TB treatment regimens. Investigating a retreatment regimen that can shorten duration of therapy is central to enhancing programmatic outcomes and this study is commensurate with this goal. Treatment default is associated with length of treatment, thus shortening treatment duration could improve outcomes, and reduce labour and financial implications of national TB control programs especially in countries with a high TB incidence. This study will explore an alternate retreatment regimen suitable for a national TB control program in a TB-HIV endemic setting.

## **10.0 HUMAN PARTICIPANTS**

### **10.1 Patient Recruitment**

Patients will be recruited from various health care facilities. Recruiters will be stationed within the TB facility and potential patients can be approached through several mechanisms:

HCT services – HIV testing and counselling is routinely offered at the PCZCDC which provides an ideal opportunity to conduct pre-screening

Each Health Care Facility has an in house National Health Laboratory Service. All new patients with a positive smear and GeneXpert Rifampicin sensitive can be identified at the laboratory and followed-up by a CAPRISA recruiter based at the facility. CAPRISA Recruiters can also identify patients with a past history of TB and the CAPRISA site can perform a GeneXpert and smear testing.

Clinic referrals - Clinicians or Professional Nurses at the facility will be trained on the study protocol and will refer patients for enrolment.

## 10.2 Ethics

Existing WHO and South African TB treatment guidelines recommend the provision of streptomycin as part of TB retreatment standard of care. However, both sets of guidelines are currently being revised, with WHO and the South African government indicating that streptomycin will no longer be recommended for TB retreatment in the next iteration of their respective guidelines (personal communications: Richard Chaisson, STOP TB working group; Norbert Ndjeka, SA National Director MDR TB). Some high TB burden countries have already successfully removed streptomycin from their NTP guidelines <sup>49</sup>. This proposed study could provide the evidentiary basis for such a policy shift in South Africa and elsewhere.

## 10.3 Regulatory and ethical review

The study will be conducted under the oversight of the University of KwaZulu-Natal, Nelson R Mandela School of Medicine Biomedical Research Ethics Committee (BREC) and the South African Medicines Control Council (MCC). The study protocol will be submitted to the ethics committee and regulatory entities by the Principal Investigator and reviewed and approved by the ethics committee prior to study initiation. The investigator will provide progress reports and all other information required by the ethics committee/regulatory institutions to conduct its reviews. On approval of the study we will register the study with SANCTR (South African National Clinical Trials Register). We will also seek approval for the study from the eThekweni Municipality.

## 10.4 Informed consent process

Written informed consent will be obtained from each study participant prior to screening and enrolment (see Appendix I). Written informed consent will also be obtained for long-term specimen storage and possible future analyses. However, consent for specimen storage is not a pre-condition for study participation. Participants will be provided with a copy of their informed consent forms if they wish to receive them.

Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be translated into *isiZulu* and the accuracy of the translation will be verified through independent back-translation.

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

## 10.5 Participant Confidentiality

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

## **10.6 Good Clinical Practice**

The study will be carried out according to ICH-GCP and South African Good Clinical Practice Guidelines (SA GCP). The Principal Investigator and/or designee will ensure that the study staff are conducting the trial in accordance with SA GCP and ICH-GCP guidelines, ensure appropriate human subjects training for all study staff and safety of all trial participants. The study protocol and patient informed consents and all future revisions of these latter documents, will be reviewed and approved by the UKZN Biomedical Research Ethics Committee (UKZN BREC) and South African Medicines Control Council (MCC) prior to implementation. Quality control officers will perform daily quality checks on patient data and a Data manager will oversee the maintenance and completeness of the patient data.

All Serious Adverse Events (SAE's) will be reported to UKZN BREC and MCC within 7 business days of site awareness. A Safety Monitoring Committee (SMC) will meet annually to analyse and discuss safety data and make recommendations for the continuation of the trial and patient care.

## **11.0 DATA MANAGEMENT**

The entry, storage and cleaning of study data will be conducted under the oversight of the CAPRISA Data Management core.

### **11.1 Data Collection and Methods**

Case Report Forms (CRFs) will be provided for each patient. At screening participants will be issued a Screening Identification number (SID) by the site. At enrolment participants will be identified by a patient identification number (PID) provided by the CAPRISA Data Management Center. This PID is used on all CRFs to identify the participant for the duration of the study.

Data will be collected at scheduled clinic visits. Patients will be required to attend at the clinic for a screening visit and if found to be eligible, informed consent will be administered and the patient will be enrolled into the study. Post enrollment visits will be scheduled once a month for the Treatment phase of the study.

### **11.2 Information management and analysis software**

CAPRISA uses the DataFax system to store data electronically. The current version of DataFax use is Version 4.1

Statistical Analysis Software (SAS) is used for analysis purposes. The current version in use is version 9.3.

### **11.3 Data entry, editing and management, including handling of data collection forms, different versions of data**

Instructions concerning the recording of study data on CRFs will be provided by the CAPRISA Data Management core. Completed CRFs must be checked by the designated on-site Quality Control officer and upon approval, must be submitted via fax into the DataFax system. CAPRISA Data encoders and Data Managers located at the Nelson R. Mandela School of Medicine verify and validate the patient data. Quality control reports are produced, and approved data then added to the study database according to CAPRISA data management (SOPs) Study Operating Procedures.

It is the responsibility of the CAPRISA data management core to assure the quality of computerized data for the study. Study staff will be trained in source documentation requirements in accordance with the CAP011 SOP for Source Documentation and in proper forms completion techniques.

Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis. Analyses will be conducted by study statisticians.

#### **11.4 Data Storage**

Original and DataFax electronic copies of study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the CAPRISA eThekweni CRS. The forms will be stored in an access secured, double-locked, fire and waterproof room. Upon completion of the study, and finalization of the database for analysis, the original forms will be bound and kept off-site (separate site) for long-term storage. CAPRISA has a standing agreement with Metrofile to archive large amounts of documents. CRF data on the DataFax server will be accessible to the study staff and the statistician in a read-only mode. The data management team will have write-access, with access being restricted by passwords and validation levels. Study staff that has access to the data on the computer systems will be trained in how to access the system and the importance of system security. All information will be backed-up at regular intervals, and backups will be stored in file cabinets or secure areas with limited access

#### **11.5 Quality control/assurance**

A quality check of the study forms will be conducted before the forms are data faxed. The QC procedures will specify the following types of checks:

- There are no illegible handwritten items, spelling errors, etc.
- Responses are clearly within designated spaces.
- All fields are completed with participant data or reason for no data is noted in or near the field.
- The participant's PID is recorded on all pages of the forms.
- The CAPRISA laboratory manager will also be responsible for checking that all the laboratories involved in the study are complying with QA procedures. The CAPRISA pharmacist will check that all drug related documentation meets Good Clinical Practice (GCP) requirements for drug accountability.

QA/QC of data will be undertaken according to the SOPs.

## **12.0 BIOHAZARD CONTAINMENT**

As the transmission of HIV and other pathogens can occur through contact with contaminated needles, blood, blood products, and other secretions, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and collection of other specimens and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

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

### 13.0 REFERENCES

1. Espinal MA, Laserson K, Camacho M, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. *Int J Tuberc Lung Dis* 2001;5:887-93.
2. W.H.O. Global Tuberculosis Control 2011. Geneva, Switzerland [http://www.who.int/tb/publications/global\\_report/2011/gtbr11\\_fullpdf](http://www.who.int/tb/publications/global_report/2011/gtbr11_fullpdf) 2011.
3. W.H.O. Global Tuberculosis Control 2008. Surveillance, Planning, Financing. vol 2008.
4. W.H.O. Treatment of Tuberculosis Guidelines. 4th edition. Geneva, Switzerland [http://whqlibdoc.who.int/publications/2010/9789241547833\\_engpdf](http://whqlibdoc.who.int/publications/2010/9789241547833_engpdf) 2010.
5. Rouillon A. The Mutual Assistance Programme of the IUATLD. Development, contribution and significance. *Bull Int Union Tuberc Lung Dis* 1991;66:159-72.
6. Menzies D, Benedetti A, Paydar A, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS Med* 2009;6:e1000150.
7. Jones-Lopez EC, Ayakaka I, Levin J, et al. Effectiveness of the standard WHO recommended retreatment regimen (category II) for tuberculosis in Kampala, Uganda: a prospective cohort study. *PLoS Med* 2011;8:e1000427.
8. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*. *Int J Antimicrob Agents* 2002;20:464-7.
9. Gillespie SH, Billington O. Activity of moxifloxacin against mycobacteria. *The Journal of antimicrobial chemotherapy* 1999;44:393-5.
10. Rustomjee R, Lienhardt C, Kanyok T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2008;12:128-38.
11. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *American journal of respiratory and critical care medicine* 2006;174:331-8.
12. Ball P, Stahlmann R, Kubin R, Choudhri S, Owens R. Safety profile of oral and intravenous moxifloxacin: cumulative data from clinical trials and postmarketing studies. *Clinical therapeutics* 2004;26:940-50.
13. Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *American journal of respiratory and critical care medicine* 2009;180:273-80.
14. Nuermberger EL, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. *American journal of respiratory and critical care medicine* 2004;169:421-6.
15. Chang KC, Leung CC, Grosset J, Yew WW. Treatment of tuberculosis and optimal dosing schedules. *Thorax* 2011;66:997-1007.
16. Peloquin CA. Therapeutic drug monitoring in antituberculosis chemotherapy. *Therapeutic drug monitoring* 1999;21:426-7.
17. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007;45:1001-7.
18. Fromm MF. The influence of MDR1 polymorphisms on P-glycoprotein expression and function in humans. *Advanced drug delivery reviews* 2002;54:1295-310.
19. Van Bambeke F, Michot JM, Tulkens PM. Antibiotic efflux pumps in eukaryotic cells: occurrence and impact on antibiotic cellular pharmacokinetics, pharmacodynamics and toxicodynamics. *The Journal of antimicrobial chemotherapy* 2003;51:1067-77.
20. de Lange EC, Marchand S, van den Berg D, et al. In vitro and in vivo investigations on fluoroquinolones; effects of the P-glycoprotein efflux transporter on brain distribution of sparfloxacin. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences* 2000;12:85-93.

21. Schuetz EG, Schinkel AH, Relling MV, Schuetz JD. P-glycoprotein: a major determinant of rifampicin-inducible expression of cytochrome P4503A in mice and humans. *Proceedings of the National Academy of Sciences of the United States of America* 1996;93:4001-5.
22. Ito T, Yano I, Tanaka K, Inui KI. Transport of quinolone antibacterial drugs by human P-glycoprotein expressed in a kidney epithelial cell line, LLC-PK1. *The Journal of pharmacology and experimental therapeutics* 1997;282:955-60.
23. Shandil RK, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. *Antimicrobial agents and chemotherapy* 2007;51:576-82.
24. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *The Lancet infectious diseases* 2003;3:432-42.
25. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. *The Journal of infectious diseases* 2004;190:1642-51.
26. Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUC break points and the link to bacterial killing rates. Part 1: In vitro and animal models. *The Annals of pharmacotherapy* 2003;37:1287-98.
27. Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUC break points and the link to bacterial killing rates. Part 2: human trials. *The Annals of pharmacotherapy* 2003;37:1478-88.
28. Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012;55:1154-63.
29. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 1999;3:S231-79.
30. Hall RG, Leff RD, Gumbo T. Treatment of active pulmonary tuberculosis in adults: current standards and recent advances. *Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy* 2009;29:1468-81.
31. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2000;4:796-806.
32. Dhillon J, Fourie PB, Mitchison DA. Persister populations of *Mycobacterium tuberculosis* in sputum that grow in liquid but not on solid culture media. *The Journal of antimicrobial chemotherapy* 2013.
33. van Ingen J, Aarnoutse RE, Donald PR, et al. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011;52:e194-9.
34. McIlleron H, Wash P, Burger A, Norman J, Folb PI, Smith P. Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. *Antimicrobial agents and chemotherapy* 2006;50:1170-7.
35. Tappero JW, Bradford WZ, Agerton TB, et al. Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005;41:461-9.
36. Um SW, Lee SW, Kwon SY, et al. Low serum concentrations of anti-tuberculosis drugs and determinants of their serum levels. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2007;11:972-8.
37. Gumbo T, Louie A, Deziel MR, et al. Concentration-dependent *Mycobacterium tuberculosis* killing and prevention of resistance by rifampin. *Antimicrobial agents and chemotherapy* 2007;51:3781-8.
38. Chideya S, Winston CA, Peloquin CA, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with



- tuberculosis from Botswana. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009;48:1685-94.
39. Peyper L. Mobile phone usage in SA. *finweek corporate news*. 22 January 2013 ed2013.
  40. Bronkhorst, Q. Mobile subscribers in SA: who's eating whose lunch? 2013. (Accessed December, 2013, at <http://businesstech.co.za/news/mobile/44164/mobile-subscribers-in-sa-whos-eating-whose-lunch/>.)
  41. Skinner D, Rivette U, Bloomberg C. Evaluation of use of cellphones to aid compliance with drug therapy for HIV patients. *AIDS Care* 2007;19:605-7.
  42. Green D. South Africa: a novel approach to improving adherence to TB treatment. *Essential Drugs Monitor World Health Organisation*; 2003.
  43. Cole-Lewis H, Kershaw T. Text messaging as a tool for behavior change in disease prevention and management. *Epidemiologic reviews* 2010;32:56-69.
  44. Mukund Bahadur KC, Murray PJ. Cell phone short messaging service (SMS) for HIV/AIDS in South Africa: a literature review. *Studies in health technology and informatics* 2010;160:530-4.
  45. Ammassari A, Trotta MP, Shalev N, et al. Timed short messaging service improves adherence and virological outcomes in HIV-1-infected patients with suboptimal adherence to antiretroviral therapy. *Journal of acquired immune deficiency syndromes* 2011;58:e113-5.
  46. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet* 2010;376:1838-45.
  47. Barclay E. Text messages could hasten tuberculosis drug compliance. *Lancet* 2009;373:15-6.
  48. Cell-Life Capabilities Document. (Accessed Jan 2012, at [http://www.cell-life.org/images/downloads/Cell-Life\\_Capabilities\\_Document.pdf](http://www.cell-life.org/images/downloads/Cell-Life_Capabilities_Document.pdf).)
  49. Furin J, Gegia M, Mitnick C, et al. Eliminating the category II retreatment regimen from national tuberculosis programme guidelines: the Georgian experience. *Bulletin of the World Health Organization* 2011;Article ID: BLT.11.092320.

## APPENDIX I: IMPRESS PATIENT INFORMED CONSENT

### STUDY INFORMED CONSENT FORM

**TITLE OF STUDY: IMPROVING RETREATMENT SUCCESS (IMPRESS): An open label randomized controlled clinical trial comparing a 24 week oral regimen containing Moxifloxacin with a 24 week standard tuberculosis (TB) drug regimen for the treatment of smear-positive pulmonary TB in patients previously treated for TB**

### INFORMATION FOR PATIENTS

**Short Title:** IMPRESS

**Principle Investigator:** Dr Nesri Padayatchi

**Address** 719 Umbilo Road  
Doris Duke Medical Research Institute (2<sup>nd</sup> Floor)  
Nelson R Mandela School of Medicine,  
University of Kwa-Zulu Natal,  
Durban, 4013

**Telephone** 031 260 4555

**Regulatory Authority:** Medicines Control Council (MCC)

**Ethics Committee:** University of KwaZulu Natal Biomedical Research Ethics Committee  
(UKZN BREC)

**Instructions:**

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

**INTRODUCTION:**

Dear Sir/Madam,

Hello and thank you for taking time to read this information. You are being invited to take part in a research study. Research is a way of finding the answer to a question. Before you decide to participate, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Feel free to ask us questions if there is anything that is not clear or if you would like more information. You are completely free to choose whether or not you wish to take part. Please take your time to decide.

We have approached you to take part in this study because you had tuberculosis of the lung in the past and currently have another tuberculosis infection of the lung.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to compare the effects of a new type of combination of TB drugs for patients who require a retreatment for TB. There are two combinations of anti-TB drugs. Each combination comprises of four anti-TB drugs.

**Standard Combination:** Isoniazid + Pyrazinamide + Rifampicin + Ethambutol

**New Combination** : Isoniazid + Pyrazinamide + Rifampicin + Moxifloxacin

The new combination removes Ethambutol and replaces it with Moxifloxacin. Moxifloxacin has been in use throughout the world for treatment of other infectious diseases (sickness caused by germs), and there is evidence from several studies that it can be used to treat tuberculosis and may even shorten the length of TB treatment.

**WHO CAN TAKE PART IN THIS STUDY?**

If you are 18 years and older and currently have TB (of the lung) and you have had TB in the past as well, then you may qualify to take part in this study.

**IS IT NECESSARY FOR ME TO TAKE PART IN THE STUDY?**

PI: Dr N Padayatchi  
Site: CAPRISA  
Study No: CAP 011

Whether or not you take part in the study is your decision. It is a voluntary decision. You do not have to give a reason if you don't want to be in it. After reading this information and agreeing with what you have read - if you decide to take part in the study - you will be asked to sign an Informed Consent form. If you decide not to take part, there will be no loss of benefit and you will receive standard TB retreatment. If you decide to take part in the study, but change your mind later, you will be free to withdraw from the study at any time. If you withdraw from the study it will not affect the quality of your medical care; you will be given standard TB treatment.

## **WHAT DOES THE STUDY INVOLVE?**

The study is in three parts:

Part 1: The screening phase

Part 2: The treatment phase

Part 3: The follow-up phase

## **WHAT DO I HAVE TO DO IF I PARTICIPATE IN THIS STUDY?**

### **Part 1: The screening phase**

The first part is called “screening phase” when we will perform tests to check whether you are suitable to participate in the study. The tests will include taking your medical history (your health in the past), performing a medical examination, a chest X-Ray if required and sputum (material that you will cough up) collection which is for TB investigation. Blood tests will be performed to make certain that there are no abnormalities (problems) that would prevent you or cause harm to you from entering the study. A test will be done to check if the common TB medicines are likely to be effective against the bacteria (type of germ) causing your TB.

It is important for you and the study staff to know your HIV status. This is to determine if you require treatment for HIV which is provided free of charge. A HIV test will be performed with pre- and post-test counselling (a study counsellor or nurse will discuss this with you to guide you about HIV-AIDS and related test procedures). If your HIV test is positive you will be started on HIV treatment if you are not on HIV treatment already.

If your HIV test is negative, we will encourage you to repeat the test as outlined in Attachment A. The window period is a time when the HIV is not detectable because the infection is still new. If you become HIV positive after you have entered the study, you will be seen by the study doctor and started on ARV's. You will also be required to produce blood for storage.

The result of the HIV test will not affect your chances of being enrolled in the study.

The blood tests at this stage will require approximately 3 or 4 teaspoons of blood. If you are a woman of childbearing age a urine pregnancy test will be conducted. If there are no major abnormalities (health problems) and you are willing to proceed further, you can join the study.

## Part 2 & 3: The treatment phase & follow-up phase

At this stage - all patients participating in the study are divided into 2 arms and each arm is given a different combination of TB treatment. One of these arms is the standard TB treatment and the other the New TB treatment combination. The results of the study shall be compared to see if one treatment is better than the other. The best way of fairly dividing people into arms is to use what is called “random allocation”. The process is the same as flipping a coin or rolling a dice. In this study, treatment arms for each patient are written in a sealed envelope. When it is your turn to be enrolled a member of the study team will select an envelope on the day of your enrolment and you will be informed which treatment arm you have been allocated to. You will have an equal chance of receiving any one of the 2 treatments. Neither you nor the study staff can choose which treatment arm you will be allocated. At the study entry visit, you will be assigned to one of these two treatment arms:

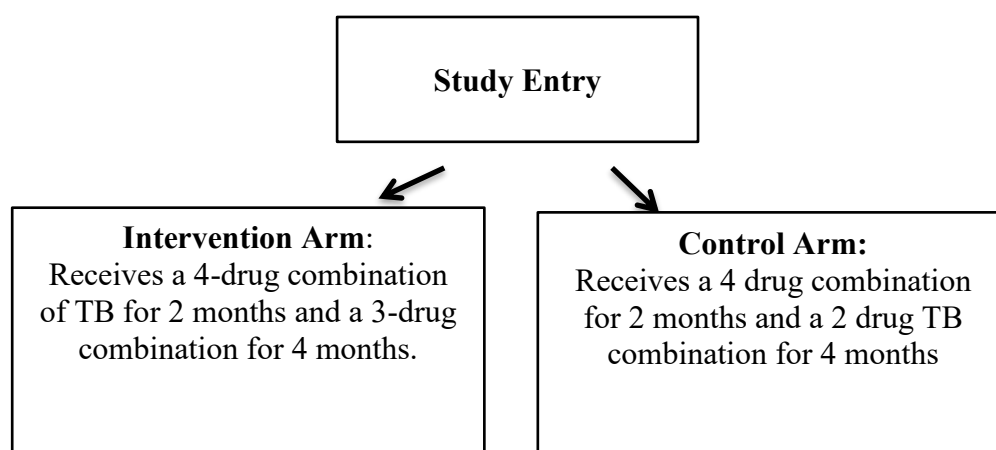


Figure 1: Patient Allocation to Study Groups

If you are placed into Intervention Arm you will be expected to take a combination of 4 drugs for the first 2 months, thereafter take a combination of 3 TB drugs for 4 months. If you have been placed into Control Arm, you will be required to take a combination of 4 drugs for the first 2 months, and then 2-combination drugs for a further 4 months. Your test results will be checked by the doctors and the doctor may give you more TB drugs. This is shown in Figure 1. While you are taking Isoniazid you will also be given pyridoxine (vitamin B6). This is a food supplement that helps to prevent side effects of the drug Isoniazid. CAPRISA will provide the pyridoxine free of charge.

After you have successively completed your treatment, you will need to come back to the clinic once every 2 months for 12 months. This will allow the medical staff to monitor the effects of the drugs on your TB infection.

## WHAT IS THE DURATION OF THE STUDY?

If you are allocated to Intervention Arm the total study duration is approximately 18 months

If you are allocated to Control Arm the total study duration is approximately 18months.

It is possible that your time in the study may be extended if there is a problem with completing all the required doses of your TB medication or if the study doctor decides to extend your treatment based on your laboratory results.

## **HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

A total of 330 patients are expected to participate in the study.

## **USE OF STORED SAMPLES**

Samples will be collected and stored for future research use. The research team may use these samples to confirm test results or to do an additional new test if required. Your samples will not be sold or used in other products that make money for researchers. Should you decide not to have your samples stored this will not affect your ability to take part in the study. Your decision will not affect the quality of care you receive at the clinic

To protect your identity your sample container will not have your name or any information that may identify you. Only your patient number will be used on sample containers. If you do not agree, then samples for storage will not be collected. If you agree now and later change your mind, your sample will not be used for future testing. No matter what you decide, it will not affect your participation in the study and this will not affect the quality of care you receive from study staff.

\_\_\_\_\_ YES, I agree to have my samples stored

\_\_\_\_\_ NO, I do not agree to my samples being stored

The stored samples may be used for future research, to confirm test results, or to do additional testing. Your samples will not be sold or used in products that make money for the researchers. Any studies that use your samples will be reviewed by the Biomedical Research Ethics Committee of the University of KwaZulu Natal.

The researchers do not plan to contact you or your regular doctor with any results that are done on the stored samples after the study has been completed.

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

## **LIPOARABINOMANNAN SUB-STUDY**

You will be required to provide urine samples at baseline, as well as at 2 Months, 5 months and at the end of your tuberculosis treatment. The purpose of this study is to determine if urine can be used to detect tuberculosis. Each urine sample will then be tested in a laboratory. When this is done the urine sample will be stored in a freezer for future testing.

## **PHARMACOKINETIC SUB-STUDY:**

You are invited to take part in the pharmacokinetic study within the IMPRESS study. The purpose of this study is to measure the amount of specific TB drugs in your blood and will add information to the IMPRESS study.

Your decision to participate in this additional study, or not, will not affect your participation in the IMPRESS study.

Before you agree to take part in the study or not it is important to understand the procedure, risks, benefits and discomforts.

Procedures:

If you decide to take part in this study:

For Intervention Arm participants:

You will be requested to undergo additional blood tests at 3 study visits (either Week 4 and/or Month 2, Month 6 and Month 7 or one month after completing TB treatment). You will also be requested to return to the study clinic the morning after these study visits to do an additional blood test.

You will be requested to take one additional dose of Moxifloxacin after the completion of your TB treatment at Month 7 or one month after completing TB treatment.

The blood tests will require about 4 teaspoons of blood at each visit.

For Control Arm participants:

You will be requested to undergo additional blood tests at Month 2. The blood tests will require about 2 teaspoons of blood at each visit.

The study team will arrange a time for the blood sampling. On the appointed day you need to arrive at the study clinic early in the morning. It is important NOT to take any TB medicines before your arrival at the study clinic. You will be given your TB treatment at the study clinic.

\_\_\_\_\_ YES, I agree to take part in the pharmacokinetic sub-study

\_\_\_\_\_ NO, I do not agree to take part in the pharmacokinetic sub-study

## COMPUTERIZED DISPENSING AND CELLPHONE TECHNOLOGY: INNOVATIVE TOOLS TO ENHANCE PATIENT ADHERENCE, TRACKING AND RETENTION

As a participant in the IMPRESS Study, you will also be offered the opportunity receive text messages reminders sent to your cell phone reminding you about appointment dates, missed appointments and/or medication use.

Three types of sms's may be sent:

- A sms reminder of the clinic appointment date that will be programmed to go out 3 days ahead of the scheduled appointment, which will read as follows: *"Please do not forget your appointment at CAPRISA clinic in three days' time"*.
- For those participants who are included in the pharmacokinetic sub-study only, an sms will be sent out the evening before a scheduled visit, which reminds the patient not to take an evening/morning dose, prior to sample collection at the clinic for pharmacokinetic (PK) study the next morning: *"Please do not take your TB medication the night or morning before coming to the clinic. Carry TB drugs with you to be taken at the clinic"*.
- A sms to prompt patients who miss their appointment to return to the clinic that will read as follows: *"You have missed your appointment at CAPRISA clinic. Please return to the clinic as soon as possible"*.
- An motivational broadcast sms to enhance patient compliance by re-enforcing adherence, programmed to be sent one week after enrolment, and periodically thereafter: at the end of month 1 of treatment and then at the beginning of the continuation phase of TB treatment, which will read as follows: *"TB can be cured and the spread of TB stopped if the full course of treatment is taken correctly, so that people can lead fuller, safer and healthier lives."*

Do you consent to receiving these SMS's:

\_\_\_\_\_ YES, I agree

\_\_\_\_\_ NO, I do not agree

### What are the likely situations where my participation in the study may be terminated?

Here are few examples of situations under which your participation in the study may be terminated:

- i) Your doctor is of the opinion that your TB treatment is going to fail (Treatment failure).
- ii) Review of your health suggests that further participation in the study may cause you more harm than benefit.
- iii) You are missing a number of clinic visits and repeatedly do not follow study instructions and not taking study drug as per the directions and this may result in more harm than benefit.



iv) The study is cancelled by the Medicines Control Council (MCC), or the University of KwaZulu Natal Biomedical Research Ethics Committee.

v) A Safety Monitoring Committee (SMC) recommends that the study be stopped early. The SMC is a group of experts who are not involved in the study, but who monitor it and look after the safety of patients. This group meets once a year and makes recommendations for the study.

There may be other similar circumstances as well.

The study may be suspended in following cases:

- i) Reports of severe and significant side effects.
- ii) Reports suggest that the new regimen under trial is not effective in treating TB.

### **WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?**

If you choose not to enter the study then you may access TB treatment from the local government clinic. The care that people who go into Control Arm receive on study is about the same as what you would receive outside the study. Certain TB drugs and HIV drugs, laboratory tests to monitor how well these drugs are working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

For TB care, the clinic staff can refer you to the Prince Cyril Zulu Communicable Disease Clinic or another clinic providing for free TB investigation and treatment. This clinic should also provide HIV medication service to eligible patients.

The CAPRISA AIDS Treatment Programme based at the CAPRISA clinic, provides a free ARV service and you may access your ARVs here.

Also, CAPRISA clinicians can assist you with accessing HIV and TB medication at your nearest government clinic.

### **WHAT ABOUT CONFIDENTIALITY?**

The study research team will give you a unique number once you are enrolled into the study. A different number will be given for each participant in the study. This unique number and not your name (or any other information that could be used to identify you) will be used for all of your study-related records. Your medical records and the list of names, addresses and code numbers will be kept in a locked room. Only the study staff will have access to these records. Any publications of this study will not use your name. The site will attempt to keep your personal information confidential. However, we cannot promise complete confidentiality. Your personal information may be disclosed if required by law. Your details may be seen by the sites ethics committee, Human Research Protection, study monitors, and drug companies that support this study.

## **WHAT ARE THE RISKS AND DISCOMFORTS ASSOCIATED WITH THIS STUDY?**

### TB DRUGS (Refer to Attachment B)

The TB drugs may have some side effects. Some of these side effects are listed in Attachment B. This list includes more serious and common side effects experienced by the study drugs. If you have any questions concerning any additional drugs you may be put onto during your course on this study, you can ask any of the clinical staff at the CAPRISA site.

### Risks in Blood Drawing:

During certain study visits, the staff nurse will draw blood from you. Taking blood may cause some discomfort, bruising or bleeding at the site where the needle enters your body. You also may feel lightheaded and in a rare case faint. The area also may become infected.

## **WHAT HAPPENS IF I BECOME PREGNANT?**

If you are pregnant or breastfeeding you will not be allowed to take part in this study because the effects of the study drugs on a baby still in the womb and babies being breast fed, is unknown. If you are women and you are having sex, you must use two reliable methods of birth control whilst on the study. This will be discussed with you by the study staff. The methods of contraception include:

- Male or female condom with or without a spermicidal agent (cream or gel that kills sperms)
- Diaphragm or cervical cap with a spermicide
- IUD (Intrauterine device) or hormone based contraception.

If you think you may be pregnant at any time during the study, please tell the study staff right away. The study staff will talk to you about your choices.

## **WHAT ARE THE BENEFITS ASSOCIATED WITH THE STUDY?**

If you decide to take part in this study, there may be a direct benefit to you, but no guarantee can be made. Medical staff at the CAPRISA site will follow your health more closely which may help you feel better. You also will be receiving free treatment and medical care.

## **WILL I RECEIVE ANY PAYMENT?**

Participants enrolled into this study will be reimbursed R150 for every study required scheduled visit. See Attachment A for required study visits. For all split, staff initiated, interim and unscheduled visits, you will be reimbursed R50.

## **WHAT ARE THE COSTS TO ME?**

There will be no cost to you for the study related visits, physical examinations, laboratory tests or other procedures.

## **WHAT HAPPENS IF I AM INJURED?**

Based on what we know now, it is unlikely that you will be injured as a result of being in this study. If you are injured as a result of being in this study, you will be given immediate necessary treatment for your injuries at the CAPRISA Clinical Research Site. You will not have to pay for this treatment. You will be told where you may receive additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

If you become injured as a result of being in this study, you will be given immediate treatment for injuries, and be referred for further treatment, if necessary. The CAPRISA Clinic has taken out an insurance policy for this study. Should you acquire an injury that is as a result of the study, please inform the study staff immediately or contact the persons listed at the end of this form. A CAPRISA staff member will assist you with any valid insurance claims.

## **WHAT ARE MY RIGHTS AS A VOLUNTEER IN A RESEARCH STUDY?**

You can decide whether or not you wish to take part in this study. If you choose not to take part in the study, the care you would normally receive will not be affected. You can also leave the study if you feel comfortable doing so.

The site staff will tell you about any new information from this study (or other studies using similar drugs) that may affect your health, welfare, or willingness to study in this study.

## **WHAT IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about this study or a research-related injury, contact any of the following persons:

**Dr Nesri Padayatchi**

**CAPRISA Deputy Director**

**Tel: 031 260 4574**

**Fax: 031 260 4566**

**E-mail: [Padayatchin@ukzn.ac.za](mailto:Padayatchin@ukzn.ac.za)**

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

**BREC Administrator or Chair - for reporting of complaints/problems-**

**Biomedical Research Ethics Committee**

**Private Bag X54001**

**Durban**

**4000**

**Tel: +27 31 260 4769**

**Fax: +27 31 260 4609**

**Email: [BREC@ukzn.ac.za](mailto:BREC@ukzn.ac.za)**

SIGNATURE FOR IMPRESS INFORMED CONSENT

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

\_\_\_\_\_

Participant's Name (print)	Participant's Signature	Date
----------------------------	-------------------------	------

\_\_\_\_\_

Study Staff Conducting Consent (print)	Study Staff Signature	Date of Discussion
---	-----------------------	--------------------

\_\_\_\_\_

Witness's Name (print) (As appropriate)	Witness's Signature	Date
--	---------------------	------

### ATTACHMENT A: Schedule of Visits

Procedures	Screening	Baseline	Week			Study Months															
			2	4	6	2	3	4	5	6	7	8	10	12	14-24 ( <sup>2</sup> monthly)	End TB Treat <sup>6</sup>	Recurrence	Termination	Time of IRIS	Time of seroconversion	
Inclusion & Exclusion Criteria		X																			
Informed Consent	X																				
Randomization		X																			
HIV test (performed monthly for HIV negative participants)	X <sup>1</sup>			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical , Medication and TB History & Physical Exam	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals (including Pregnancy test )	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception confirmation	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X		X		X	X	X	X	X	X	X	X	X		X					
GeneXpert	X																				
Sputum Smear	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Culture : <b>INTERVENTION ARM:</b> until 6 months		X	X	X	X	X	X	X	X	X					X	X	X				
Culture: <b>CONTROL ARM:</b> until 6 months		X	X	X	X	X	X	X	X	X					X	X	X				
Susceptibility		X				X				X*					X*		X	X			
PAXgene for SHIP Study		X				X				X					X	X	X	X			
Urine (Lam Testing)		X				X			X	X						X					
Chest radiograph		X <sup>2</sup>					X			X						X	X				
ECG **		X				X		X		X											
Vision testing (Snellen and Ishihara) <b>Control Arm only</b>		X				X															

Procedures	Screening	Baseline	Week			Study Months																	
			2	4	6	2	3	4	5	6	7	8	10	12	14-24 (2 monthly)	End TB Treat <sup>6</sup>	Recur rence	Termi nation	Time of IRIS	Time of serocon version			
AST, ALT, Bilirubin, Hb, platelets, & Full blood count, Creatinine clearance, potassium, total protein, alkaline phosphatase	X	X <sup>2</sup>				X		X		X							X	X	X	X	X		
CD4 Count ( <b>HIV Infected patients only</b> )	X					As per SA HIV guidelines																X	
Viral Load ( <b>HIV Infected patients only</b> )	X																				X	X	
HBsAg	X																						
PK Samples (Intervention Arm)			X		X <sub>3</sub>				X	X <sub>4</sub>													
PK Samples (Control Arm)					X																		
Specimen Storage		X	X		X		X						X				X				X		
PBMCs***		X <sup>5</sup>				X				X					X	X	X	X	X	X	X		

1: HIV Testing is required at screening for all potential participants. Thereafter, monthly HIV testing will be required for HIV negative participants only.

2: A Chest Radiograph/ Bloods will be repeated if they are more than 14 days old

3: PK blood samples, in the intervention arm only, will be taken once during the intensive phase of TB treatment at either Week 4 **OR** Month 2 (**PK bloods may be repeated at Month 2 if these were not taken, incorrectly done or incomplete at Week 4 OR at the discretion of the investigator**), and at the end of TB treatment (Month 6)

4: Additional PK samples will be taken at M7 (or the first visit after if Month 7 is missed) in Intervention Arm before and after the ingestion of the single additional dose of Moxifloxacin. This additional PK sample may be deferred to month after TB treatment completion on participants who have TB treatment extended beyond 6 months

5: If PBMCs are not collected at baseline samples may be taken at Week 4 or Month 2

6. End of TB Treatment visit will be conducted with 7 days of completion of TB treatment.

\* Samples will be collected and stored for future susceptibility testing,

\*\*ECG's will be done at baseline, Month 2, Month 4 and Month 6. ECG's will be performed 2 monthly during treatment with Moxifloxacin

\*\*\*Additional PBMC's will be collected at IRIS and at the time of seroconversion

## ATTACHMENT B - Study Drug Side Effects

Drug	Common Side Effects
<b>Any</b>	<p>Changes in body shape, such as:</p> <ul style="list-style-type: none"> <li>• increase in fat around the waist and stomach</li> <li>• increase in fat on the back of the neck</li> <li>• thinning of the face, legs, and arms</li> <li>• breast enlargement</li> </ul>
<b>Isoniazid</b>	<ul style="list-style-type: none"> <li>• changes in vision</li> <li>• clumsiness or unsteadiness</li> <li>• changes in the colour of urine</li> <li>• loose or watery stools</li> <li>• loss of appetite, weight loss, nausea (feeling sick to the stomach) and vomiting</li> <li>• pain in upper abdomen</li> <li>• skin rash</li> <li>• stools lighter in colour</li> <li>• fever</li> <li>• tingling and numbness in the hands and feet, especially if extra vitamin B6 is not taken with INH; this risk is increased in malnourished individuals and pregnant women.</li> <li>• weakness and fatigue</li> <li>• yellowing of eyes or skin</li> </ul> <p>In general, these side effects are temporary. There may also be an increase in some liver function tests indicating that there may be some damage to the liver.</p>
<b>Pyrazinamide</b>	<ul style="list-style-type: none"> <li>• Markedly reduced appetite</li> <li>• Nausea</li> <li>• Flushing</li> <li>• liver inflammation</li> <li>• vomiting</li> <li>• joint pain</li> <li>• elevated levels of uric acid in the blood which may lead to gout</li> <li>• drug rash</li> </ul> <p><u>Rarely</u></p> <ul style="list-style-type: none"> <li>• gout</li> <li>• sensitivity to light</li> </ul>
<b>Rifampicin</b>	<p>Rifampicin is commonly prescribed in the United States and worldwide to treat TB, and is generally well tolerated.</p> <p>Rifampicin turns urine, sweat, sputum, and tears a red-orange color. The red-orange color in urine may stain undergarments. Soft contact lenses may be permanently stained by Rifampicin.</p> <p>Less common side effects include:</p> <ul style="list-style-type: none"> <li>• Hepatitis (inflammation of the liver). This has caused deaths in patients who already had liver disease or who were taking other drugs that were toxic to the liver.</li> </ul>



	<ul style="list-style-type: none"> <li>• increases in liver function tests</li> <li>• increased bilirubin, which may be associated with yellowing of the eyes</li> <li>• upset stomach, vomiting, and diarrhoea</li> <li>• abdominal pain</li> <li>• reduced levels of some of your body's hormones</li> <li>• reduced levels of calcium and phosphate in blood</li> <li>• decreased effectiveness of hormonal contraceptives and many other medications</li> <li>• reduced blood cell counts</li> <li>• headache</li> <li>• rash and itching</li> <li>• fever</li> <li>• kidney failure</li> </ul>
<b>4-drug Combination</b>	<p>The most common side effects of standard therapy with INH, Rifampicin, Ethambutol and Pyrazinamide are similar to those that people have with the individual drugs.</p> <ul style="list-style-type: none"> <li>• nausea</li> <li>• vomiting</li> <li>• fever</li> <li>• rash</li> <li>• joint pain</li> <li>• liver toxicity</li> <li>• elevated uric acid levels in blood, which rarely lead to gout</li> <li>• tingling and numbness in the hands and feet unless extra vitamin B6 is taken; this risk is higher in malnourished individuals and pregnant women.</li> <li>• changes in vision</li> </ul> <p><u>Rarely</u> gout</p>
<b>Ethambutol</b>	<ul style="list-style-type: none"> <li>• Inflammation of nerves in the eyes</li> <li>• Joint pain</li> </ul> <p><u>Rarely</u></p> <ul style="list-style-type: none"> <li>• liver inflammation</li> <li>• rash</li> <li>• elevation of uric acid in the blood, which may lead to gout</li> </ul>
<b>Moxifloxacin</b>	<ul style="list-style-type: none"> <li>• nausea</li> <li>• diarrhoea</li> <li>• pain in the belly</li> <li>• headache</li> <li>• dizziness</li> <li>• mild increase in liver enzymes</li> </ul> <p><u>Rarely</u></p> <ul style="list-style-type: none"> <li>• inflammation (swelling/tenderness/redness/pain) of the gut</li> <li>• allergic reaction</li> <li>• loss of smell and mental/mood changes</li> </ul>

Very Rarely

- irregular heartbeats
- fits
- severe allergic reaction
- tendon inflammation
- arthritis
- kidney failure
- myasthenia (weakness of eye and other muscles)

Life threatening

- Liver inflammation leading to liver failure
- severe skin rash with blistering and peeling