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Piloting TUTT-PT: Targeted universal TB testing with simultaneous TPT prescribing among people living with HIV in South Africa

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Implementing Partner: PHRU, South Africa

Principal Investigator: Christopher Hoffmann

South Africa Principal Investigator: Neil Martinson

Statement of Compliance

The study will be carried out in accordance with the design and specific provisions of this Human subjects ethics-approved protocol, with the ethical principles that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements by the following:

- Declaration of Helsinki
- ICH GCP E6
- Completion of Human Subjects Protection Training

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the Human Research Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to Human Research Ethics Committee any changes in research activity and all unanticipated problems involving risk to human subjects or others.

STUDY SUMMARY

Background: The overarching goal of this proposal is to contribute to safely increasing TB preventive therapy (TPT) uptake in the context of a new South African policy of universal TB testing at ART initiation. TB is the leading infectious cause of death globally; South Africa has one of the highest incidences of TB worldwide (513 cases/100,000 individuals in 2021).[1] TPT forms a cornerstone of World Health Organization (WHO) and South African TB control guidelines. The Fedisa PreventTB study (R01AI150432) is testing a behavioural economics approach to increase TPT prescribing to people living with HIV (PLHIV) in a cluster-randomized trial in 36 public-sector health facilities in South Africa. In preliminary analyses, we have observed overall TPT delivery reaching 51% of PLHIV (among 52,000 patients assessed). While the study is ongoing, the combined data show a marked year to year increase in TPT prescribing at ART initiation from approximately 23% in 2017 to 69% in 2022. Although receipt of TPT has increased, barriers remain.

In 2023, the South African Department of Health introduced targeted universal TB testing (TUTT) at ART initiation (irrespective of the presence of TB symptoms). Guidelines regarding TPT initiation in the setting of TUTT are conflicting - recommending either (1) delaying TPT initiation for all patients until a negative TB test result is returned[2] or (2) delaying TPT only for those patients with a positive TB symptom screen.[3] The new TUTT approach along with ambiguity in the timing of TPT initiation has the potential to substantially reduce timely TPT initiation – missing the period of highest TB risk. In modelling approaches for TB screening and TPT delivery, we found that waiting for a sputum result could decrease TPT prescribing from the current level to approximately 17-31%.[4] *A novel alternative is to provide TPT at the time of TB testing to all patients initiating or re-initiating ART (TUTT-PT)*. Those who test positive for TB (5-8% of patients) would be promptly contacted and switched to anti-TB treatment. Our model suggests that this strategy could ensure that almost 90% of patients receive TPT and are tested for TB simultaneously. The viability of such an approach depends on demonstrating the safety and effectiveness of TPT for all vs the standard of care. Guiding the optimal implementation strategy for TPT delivery - balancing high-levels of TPT prescribing with rapid diagnosis and treatment initiation for active TB disease - is essential to ensure the continued success of South Africa's TPT program.

The Fedisa PreventTB study has a currently active research platform ideal for comparing these two strategies to optimize TPT delivery. We are proposing a one-year study built onto Fedisa PreventTB to compare the proposed novel approach of universal TPT to the standard approaches to inform further TPT policy and optimize the effectiveness of the Fedisa PreventTB behavioral economics approach in light of the new TB testing approach.

Aims: To pilot test the effectiveness and safety of targeted universal TB testing with simultaneous TPT (TUTT-PT) to increase TPT initiation among PLHIV initiating (or re-initiating) ART and to characterize clinic level implementation determinants among health care workers.

Methods: This non-randomized pilot evaluation is designed to evaluate the safety and effectiveness of universal TB testing with simultaneous TPT provision to people living with HIV initiating or re-initiating ART in South Africa.

Significance: Early identification and treatment of active TB disease is critical to reduce transmission of TB. However, universal TB testing for newly initiating or re-initiating ART clients may result in delayed and/or decreased TPT prescribing at a time of high TB risk for PLHIV. Universal TB testing combined with universal TPT prescribing would ensure simultaneously high rates of TB prevention, testing, diagnosis, and treatment initiation for this high-risk group.

Key Personnel

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1 Background

1.1 Introduction

1.1.1 HIV and TB in South Africa. South Africa is home to over 7.5 million people living with HIV (PLHIV), more than any other country globally.[5] In addition, South Africa has one of the highest incidence rates of tuberculosis (TB) worldwide, estimated at 513 cases per 100,000 individuals in 2021.[1] Since first offering antiretroviral therapy (ART) in public-sector care for PLHIV in 2004, the South African National Department of Health (NDoH) has progressively expanded treatment access by raising the CD4 count eligibility threshold until ultimately adopting a universal test-and-treat approach in 2016,[6] with same-day ART initiation following in 2017.[7] The use of ART reduces the risk of active TB disease in PLHIV;[8] however, PLHIV still account for more than half of TB case notifications in South Africa.[1] In addition to the expanded use of ART, the NDOH has also committed to reducing the burden of TB disease among PLHIV through the use of TB preventive therapy (TPT). In numerous clinical trials, TPT has been shown to reduce the risk of active TB disease and shorter intermittent regimens, such as 3 months of once-weekly rifapentine and isoniazid (3HP), have proven to be as effective as 6 or 9 months of daily isoniazid preventive therapy (IPT).[9–13] In a 2015 systematic review of 10 clinical trials providing IPT to PLHIV, an overall 35% reduction in the risk of TB was observed for patients receiving IPT vs placebo (95% CI: 0.51, 0.84), with an even greater benefit observed for those with documented latent TB infection (RR: 0.48; 95% CI: 0.29, 0.82).[14]

1.1.2 The prevalence of subclinical TB disease. In recent years, several studies in high TB-burden settings have evaluated the prevalence and clinical features of asymptomatic, or subclinical, TB using universal TB testing, irrespective of symptom status. In a 2021 review of TB prevalence surveys conducted in 23 countries across Africa and Asia, a median of 50.4% of TB disease identified in population-based surveys was identified as subclinical.[15] Studies have also reported on the prevalence of subclinical TB among PLHIV in South Africa. Among ART-naïve PLHIV tested for TB (without consideration for the presence or absence of symptoms), overall prevalence estimates of TB ranged from approximately 13%-19%.[16–20] Three studies reported that between 16-23% of confirmed TB cases were asymptomatic at the initial evaluation,[16–18] while other studies reported asymptomatic TB accounting for as low as 9% and as high as 52% of all TB.[19,20] Finally, in a study of facility-based targeted universal TB testing in South Africa for people living with HIV, those with a previous TB diagnosis in the preceding two years, and those with contact with a TB patient in the last 12 months, 55% of those who tested positive for TB reported no symptoms at the time of specimen collection.[21]

1.1.3 New approach for universal TB testing is a paradigm shift for South Africa. In the 2023 ART Clinical Guidelines, the South African NDoH called for targeted universal TB testing (TUTT) for people living with HIV as a component of the clinical evaluation for ART and TPT initiation, irrespective of symptom status.[3] However, guidelines regarding the timing of TPT initiation are conflicting – recommending either (1) delaying TPT initiation for all patients until a negative TB test result is returned[2] or (2) delaying TPT only for those patients with a positive TB symptom screen.[3] The new TUTT approach along with ambiguity in the timing of TPT initiation has the potential to substantially reduce timely TPT initiation – missing the period of highest TB risk. In modelling approaches for TB screening and TPT delivery, we found that waiting for a sputum result could decrease TPT prescribing from the current level to approximately 17-31%.[4] A novel alternative is to provide TPT at the time of TB testing to all patients initiating or re-initiating ART (TUTT-PT).

1.1.4 There is a knowledge gap regarding the potential viability, safety, and effectiveness of TUTT-PT for PLHIV initiating ART. Our model suggests that the TUTT-PT strategy of universal TB testing with universal TPT (and switch to anti-TB treatment for those who test positive for TB) could ensure that almost 90% of patients receive TPT and are tested for TB simultaneously. The viability of such an approach, however, depends on demonstrating the safety and effectiveness of TUTT-PT vs the standard of care. Guiding the optimal implementation strategy for TPT delivery - balancing high-levels of TPT prescribing with rapid diagnosis and treatment initiation for active TB disease - is essential to ensure the continued success of South Africa's TPT program.

The Fedisa PreventTB study has a currently active platform to compare these two strategies to continue to optimize TPT delivery. We will conduct a one-year study built into Fedisa PreventTB to compare the novel approach of TUTT-PT to the standard approach to inform further TPT policy and optimize the effectiveness of the Fedisa PreventTB behavioural economics approach to TPT prescribing.

1.2 Study Objectives

The overarching goal of this study is to pilot universal TB testing combined with universal TB preventive treatment initiation among people living with HIV initiating ART in South Africa; we will evaluate the feasibility, infer effectiveness and assess possible adverse events associated with this strategy. We will utilize a mixed-methods design comprising of a non-randomized pilot evaluation and in-depth interviews to achieve our study objectives.

The primary objectives are:

1. To compare the proportion of PLHIV who initiate TPT within 7 days of ART initiation based on same day TPT or not.
2. To compare the proportion of PLHIV who initiate TPT and have a subsequent positive TB test result based on same day TPT or not.
3. To estimate the safety of each TPT initiation approach based on the median time to TB treatment initiation among those who test positive for TB based on same day TPT or not.
4. To understand health care provider experiences with implementation of universal TB testing and TPT provision for PLHIV initiating or re-initiating ART

The secondary objectives are:

1. To estimate the proportion of PLHIV evaluated for ART initiation who are tested for TB within 7 days of ART initiation, stratified by symptom status.
2. To determine the prevalence of active TB disease among PLHIV evaluated for ART initiation, stratified by symptom status.
3. To estimate the median time from ART initiation to TPT initiation
4. To determine the proportion of PLHIV diagnosed with TB who remain on TPT for 7 days or longer.
5. To estimate the prevalence of TB drug resistance at TB treatment initiation, stratified by TPT use at the time of TB diagnosis.
6. To estimate the incidence rate of new TB diagnoses within 6 months of ART initiation

1.3 Significance

Early identification and treatment of active TB disease is critical to reduce transmission of TB. However, universal TB testing for newly initiating or re-initiating ART clients may result in delayed and/or decreased TPT prescribing at a time of high TB risk for PLHIV. Universal TB testing combined with universal TPT prescribing would ensure simultaneously high rates of TB prevention, testing, diagnosis, and treatment initiation for this high-risk group.

2 Methods

2.1 Study design

We are proposing **a non-randomized pilot evaluation** of a universal TPT initiation strategy within the context of TUTT implementation for PLHIV initiating or re-initiating ART. Clinics will be assigned to the novel TUTT-PT arm or standard TUTT implementation arm with the primary analysis focused on the proportion initiated on TPT within 7 days of ART start. This study will also assess the rate of new TB diagnoses, TB treatment initiation for those testing positive for TB, the prevalence of TB drug resistance at the time of TB treatment initiation, time to TPT initiation, and provider experiences with TUTT implementation and TPT provision, among others.

2.2 Study setting

This study will be conducted by PHRU in 5 public sector health facilities in the Dr Kenneth Kaunda district, North West province, South Africa that are participating in the Fedisa PreventTB study. As of 2016, the Dr Kenneth Kaunda district has a population of 742,820 with HIV prevalence estimated as 12.9%.[22] The Fedisa PreventTB study was conducted in 18 public-sector health facilities providing HIV and TB related care. Thus, the PHRU team is very familiar with the study setting and has strong relationships with the provincial Department of Health, the district and sub-district offices, and the clinic managers and staff.

2.3 Study population

All adult people living with HIV who are either newly initiating or re-initiating ART will be screened for enrolment.

Inclusion criteria:

- Adults 18 years and older
- Person living with HIV newly initiating or re-initiating ART at a participating site.
- Residing within the catchment area of the clinic and willing to be followed up at telephonically or via a home visit by a study team tracer.
- Willing and able to provide their own written informed consent.

Exclusion criteria:

- Person living with HIV stable on ART.
- Not speaking any of the languages spoken by the study team

2.4 Clinic selection

Among the 18 public sector health facilities that participated in Fedisa in the Dr Kenneth Kaunda district, 5 will be selected to participate in the study from the list of clinics below. Clinics were chosen based on the average number of PLHIV who initiated or re-initiated ART on a monthly basis in 2021 and 2022. In order to ensure we can achieve the required sample size; we will select the larger clinics (on the basis of ART (re-)initiations) for study participation. Among the five selected clinics, two clinics will be assigned to standard TUTT implementation, and three clinics will be assigned to TUTT-PT implementation.

District	Clinic	ART initiations 2021	Mean monthly initiations 2021	ART initiations 2022	Mean monthly initiations 2022
Matlosana	Majara Sephapho	230	19.2	133	14.8
Matlosana	Orkney	207	17.25	130	14.4
Matlosana	Gateway NM Pretorius PHC	201	16.8	104	11.6
Matlosana	Kanana	194	16.2	114	10.4
Matlosana	Alabama	159	13.25	162	13.5
Matlosana	Tsholofelo	146	12.2	118	9.8
Matlosana	Empilisweni	144	12	102	11.2
Matlosana	Khuma	120	10	109	9.1

2.5 TUTT-PT (intervention) arm

In the TUTT-PT arm, newly initiating or re-initiating ART clients will be referred by clinic staff after ART initiation to the PHRU study nurse for eligibility screening and enrolment. All TUTT-PT arm participants who provide written informed consent will have sputum collected for TB testing (if sputum was not already collected by the clinic staff) and will receive a clinical evaluation for the presence of TB symptoms (cough, fever, weight loss, night sweats) and serious contraindications for TPT initiation (known liver disease, high alcohol intake (men: >5 drinks/day or >15 drinks/week; women: >4 drinks/day or >8 drinks/week), or strong clinical suspicion of TB disease as evidenced by severity of symptoms, including haemoptysis, or Karnofsky score ≤50. PLHIV for whom the study nurse does not have a strong clinical suspicion of TB nor evidence of serious TPT contraindications will be referred to clinic staff for TPT initiation, irrespective of the presence or absence of TB symptoms.

2.6 Standard TUTT implementation arm

In the standard TUTT implementation arm, ART clients who initiated or re-initiated ART will be referred to the PHRU study nurse for eligibility screening, enrolment, and a clinical evaluation after the consultation has been completed. All laboratory investigations and ART and TPT prescribing will occur as per routine care in the facility prior to referral to the PHRU study nurse who will obtain written informed consent for study participation.

2.7 Safety of TUTT and TUTT-PT

A primary goal is to test the safety of universal TPT with TUTT. To maximize safety in terms of immediate receipt of appropriate anti-TB therapy, each clinic, irrespective of arm, will be supported by a PHRU study team tracer. Any participant who tests positive for TB will be immediately contacted by the tracer telephonically. Those who cannot be reached via telephone will be visited at the household by the tracer to alert the participant of their TB test result and facilitate return to the clinic for switch from TPT to anti-TB treatment (or to initiate anti-TB treatment if not on TPT). All participants who test positive for TB will have two additional spot sputum specimens collected on the date of anti-TB treatment initiation. The first specimen will be used as per routine care. The second specimen will be sent for study-specific culture and drug-susceptibility testing.

Participants who test positive for TB will be referred to clinic staff for termination of TPT and initiation of anti-TB treatment. Those with trace results on Xpert Ultra will be managed as per routine care. No further interaction between the study nurse and the participant will take place thereafter.

All participants who are prescribed TPT will be contacted 1 month after TPT initiation by the PHRU study team tracer to check for side effects and/or signs of any TPT-related adverse events. Participants who report potential side effects or adverse events will be referred to clinic staff for ongoing management. The Principal Investigator will promptly report to Human Research Ethics Committee any changes in research activity and all unanticipated problems involving risk to human subjects or others.

2.8 Outcomes and analysis

The primary outcomes are the proportion of PLHIV who initiate TPT within 7 days of ART start and the median time to TB treatment initiation for those who test positive for TB. ART initiators include clients who are ART naïve and those re-initiating ART after a lapse in treatment. Secondary outcomes are included in the table below. TB test results and TPT initiation will be ascertained from study source documents and all available data sources in the clinics, including but not limited to paper files, electronic files (Tier.NET and DHIS2), clinic registers, pharmacy records, and lab test results. Analytic approaches are described in the table below.

Table 1. Outcomes & analysis approach

	Outcomes	Data source	Statistical Test
Primary	Proportion of PLHIV who initiate TPT within 7 days of ART (re-)initiation	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Chi-square
Primary	Proportion of PLHIV who initiate TPT and have a subsequent positive TB test result	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Chi-square
Primary	Healthcare provider experiences with universal TB testing and TPT provision	In-depth interviews	N/A
Primary	Median time to TB treatment initiation for those who test positive for TB	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Kaplan-Meier
Secondary	Proportion of PLHIV evaluated for ART (re-)initiation tested for TB within 7 days of ART start, stratified by TB symptom status	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Chi-square
Secondary	Prevalence of active TB disease among PLHIV evaluated for ART (re-)initiation, stratified by symptom status	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Chi-square
Secondary	Median time from ART initiation to TPT initiation	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Kaplan-Meier
Secondary	Proportion of PLHIV diagnosed with TB who remain on TPT for 7 days or longer	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Chi-square
Secondary	Prevalence of TB drug resistance at TB treatment initiation, stratified by TPT use at the time of TB diagnosis	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Descriptive proportions
Secondary	TB incidence rate within 6 months of ART initiation	Paper files, electronic files, clinic registers, pharmacy records, lab test results	Descriptive proportions

2.9 Sample size justification

We hypothesize that TPT prescribing will be 65% in routine TUTT implementation and 80% in TUTT-PT implementation. Thus, we will enrol 200 PLHIV in TUTT clinics and 200 PLHIV in clinics where they will receive TUTT-PT (450 total) in order to detect this difference with 80% power at a 5% level of significance while accounting for clustering by clinic (a design effect of approximately 1.3). A sample size of 450 will also enable us to identify an estimated 20 new ART clients diagnosed with TB (assuming prevalence of 5%) in order to evaluate time to TB treatment initiation. In addition, throughout study implementation, we will conduct ongoing monitoring of intervention safety, defined as the number of participants diagnosed with TB who remain on TPT after diagnosis by study arm.

2.10 Clinic level implementation determinants

We will conduct in-depth interviews with health care workers who evaluate PLHIV for ART initiation, screen and test for TB, and prescribe TPT and/or anti-TB treatment. Interviews will be conducted with 20 health care workers with experience with TUTT implementation and TPT provision to understand compatibility of changes in TB screening and testing to prior processes, acceptance of simultaneous TPT prescribing to symptomatic ART clients, challenges experienced with provision of TPT and/or anti-TB treatment, and level of confidence with TPT prescribing approaches. We will seek to maximize diversity of opinions by purposively selecting from levels of providers (primary care nurses and doctors, if doctors are present in study clinics), a range of ages, men and women, and duration of practice.

Analysis: Transcripts of audio-recordings will be uploaded into qualitative analysis software for the purposes of coding and analysis. Our approach to the qualitative data will involve thematic analysis and employ both inductive and deductive coding techniques. We will first develop an *a priori* code book that reflects key analytic concepts of the Normalization Process Theory. During the process of reading and coding of transcripts using this initial coding scheme, additional codes may be added to document emerging themes of interest.

Analysis will be led by an experienced qualitative researcher (Dr Owczarzak) and will be assisted by the qualitative PHRU team. Qualitative analysis will first explore broad patterns and experiences of health care workers, and then will assess potential similarities and differences in experiences by participant characteristics, including age, sex, and level of training.

3 Study implementation timeline

	2023 Q3	2023 Q4	2024 Q1	2024 Q2	2024 Q3	2024 Q4	2025 Q1	2025 Q2
Protocol development	X							
WHREC and JHU IRB approval		X						
NHRD (provincial and district approval)		X						
Staff recruitment and training		X	X					

Study initiation activities		X	X					
Participant recruitment			X	X	X	X		
Participant follow-up				X	X	X	X	
Provider IDIs				X				
Study Close- out and data cleaning							X	X
Data analysis and write-up								X
Local and international dissemination of results (publications, conferences, policy briefs)								X

4 Data management

Data will be collected directly from participants through an enrolment questionnaire and from all available data sources in participating clinics. No data will be collected at JHU or JHU-affiliated sites.

4.1 Data collection tools

Table 2. List of data collection tools and intended use

Name of tool	Purpose	Schedule	Study arm
Screening form (S001)	Confirm potential participant meets study eligibility criteria	Enrolment	Both
Patient enrolment questionnaire (PT001)	Baseline demographic and health data collected from study participants	Enrolment	Both
Laboratory test results (LT001)	All laboratory test results	Enrolment and 3 months after enrolment	Both
TB Follow-up Visit (PT002)	To document participant follow-up visit (sputum collection, switch from TPT to TB tx) following a positive TB test result	Following positive TB test result	Both
Health Monitoring Call (HM001)	To monitor participants for any symptoms or adverse events after starting TPT	1 month after starting TPT	Both
Medical record review (MR001)	ART history, TPT history, TB diagnoses, TB treatment initiation and regimen changes, and TPT initiation	3 months after enrolment	Both
Health care worker interview guide (IG001)	Interview guide for assessing clinic level implementation determinants	3-6 months after study initiation	Both

Participant completion form (PC001)	To document patient study completion, withdrawal, and death	As needed, and at ~3 months after enrolment	Both

4.2 Database

4.2.1 Structure of the database

Data will only be collected at the PHRU site into a RedCAP database. Data will not be collected at any other sites. The quantitative study database will be built within the secure web-based REDCap™ (Research Electronic Data Capture) system. REDCap provides an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources. We will develop a separate form within REDCap for each case report form (CRF). All fields will have appropriate range-checks for validation during data-entry. Field numbers and names in the database will correspond to numbers and names on the CRF. Trained data capturers or research assistants will either directly enter data into REDCap using tablets or will manually input all data into the electronic database from paper CRFs.

Data entry validation and automatic range checks will be incorporated in most data fields to reduce data entry errors. In addition, bi-weekly electronic checks for inconsistencies within and across forms will be performed followed by source document review of any data queries that are generated.

4.2.2 Database access

Access to all databases (data entry, reporting, and extraction) is controlled by the PHRU Data Manager, JHU and PHRU Research and Project Managers, and the REDCap Database Administrator. Study personnel requiring access to the database must complete required documentation and training prior to receiving the necessary username and password. Identified data will only be captured on paper recruitment logs. Laboratory data will be abstracted from NHLS and clinical records.

4.2.3 Locking of final database

The final study database is locked to changes after the clean file form has been signed. Final storage of the database is with the production folder structure together with all the Metadata, source data and the user written programs and the version of the system used to produce the database. The folder is given a special icon to show it is locked and the available choices are restricted to reading the data.

4.2.4 Data security

All paper study records (e.g. consent forms) will be kept in a secure location accessible only to authorized study staff, investigators, and monitors.

5 Study limitations

This study has the following limitations:

- As this is a non-randomised pilot, inferences of our results will be limited.
- Some new ART clients may be unwilling or unable to provide written informed consent to participate in the study. This may result in selection bias in our study population and limit generalizability.
- The presence of a PHRU study team research interviewer may influence routine TUTT implementation and TPT prescribing in standard of care clinics. We will minimize this influence by only enrolling participants into the study after the clinical consultation has been completed.
- Some participants may not own or have access to a mobile phone which is necessary for tracing of those who test positive for TB to initiate them rapidly on anti-TB treatment. To mitigate delays in anti-TB treatment initiation, all participants will consent to a household visit for tracing purposes if they do not have or do not answer their mobile phone.

6 Appropriate care in response to study-specific findings.

Participants in both TUTT-PT and routine TUTT implementation clinics who test positive for TB will be traced by a PHRU study team tracer and initiated on anti-TB treatment. The tracer will aim to return the participant to the clinic within 72 hours of sputum collection (48 hours for return of results and an additional 24 hours to trace the participant). The PHRU study nurse will refer participants to clinic staff for switch from TPT to anti-TB treatment in TUTT-PT participating facilities and clinic staff will initiate anti-TB treatment in routine TUTT implementation clinics. All participants who test positive for TB will be requested to provide additional sputum specimens (1) as per routine care and (2) for study-specific culture and drug susceptibility testing. Those with evidence of drug resistance will be referred to a doctor for further review and drug-resistant TB treatment initiation, as necessary.

7 Protection of human participants

7.1 Regulatory approvals

This study will be conducted according to Good Clinical Practice (GCP) guidelines and completed in compliance with international and local human subject research guidelines. Approvals will be sought from the University of the Witwatersrand Human Research Ethics Committee, North West Province, and the Johns Hopkins University IRB. No changes will be made to the study protocol without approval from co-investigators from both sites.

7.2 Risks and benefits

- The primary goal of this study is to improve prescribing of TPT. Due to the nature of the intervention in which participants will be prescribed ART and TPT prior to receipt of their TB test result, irrespective of the presence or absence of TB symptoms, the risk exists that participants with active TB disease will be on INH monotherapy for a short duration of time. However, we intend to trace participants and switch them to anti-TB treatment within 72 hours of sputum collection; thus, participants later determined to have active TB disease should not be on INH monotherapy for more than 7 days (accounting for the weekend) prior to anti-TB treatment initiation. Additionally, all participants, irrespective of study arm, will provide an additional specimen for culture and drug susceptibility testing. This will enable the study team

to immediately refer any participant with evidence of drug resistance to a doctor for further evaluation and drug-resistant TB treatment initiation, if necessary.

- Among participants there is a risk of inadvertent disclosure of HIV status. This risk will be addressed through training of study staff and secure storage of all study documents.

- Among health care workers recruited for in depth interviews there is a risk of inadvertent release of comments about care proficiency. All documents and data will be confidential and securely stored. No individual level results will be provided to other health care workers, clinic management, or Department of Health personnel.

7.3 No excessive inducements for participation.

There will be no excessive inducements for the participants, except for consenting and completion of questionnaires/interviews.

7.4 The information is presented in language that is understandable to the subject population.

The Participant Information Sheet (PIS) and other study related communication is at the participant level. Additionally, the PIS will be translated into the appropriate common local languages (eg. Setswana, Sesotho and Isixhosa) spoken in North West province.

Written informed consent will be obtained from eligible patient participants and from health worker participants at times convenient to them. The consent process will be done in a private area to ensure confidentiality. Informed written consent, using Ethics Committee/IRB-approved consent forms, will be obtained by trained study personnel prior to performing any study-specific procedures. Informed consent is a process that will be initiated prior to the individual's agreeing to participate in the study and will continue throughout the individual's study participation. Potential participants will receive information about risks and possible benefits of study participation, study objectives, and procedures. Informed consent requires the legally effective signature or mark of the subject. A copy of the signed and dated informed consent document will be offered to each participant for his or her records. The rights and welfare of the subjects will be protected by emphasizing to subjects that the treatment by health care providers will not be adversely affected if they decline to participate in this study, and that they may withdraw consent at any time. The investigator will retain a copy of the signed consent forms, which may be inspected at the monitor's/auditor's request. The investigator will promptly report to the Ethics Committee/IRB of all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make changes in the research without Ethics Committee/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The informed consent process will include a verbal review of the study, provision of participant information sheets in relevant languages, review of the information sheets, and answering any questions. Participants unable to read or write will be asked to make a mark or thumbprint in the presence of a witness (verbal consent will not be obtained). Only written informed consent will allow for study participation.

Health care worker participation

Health care providers involved in ART initiation, screening and testing for TB, and prescribing of TPT and/or anti-TB treatment will be recruited for participation. Selected providers will be invited by a study team member to participate. Study information will be provided to the potential provider participant. Providers willing to participate will be asked to sign a written informed consent document in duplicate. One copy will be provided to the provider and the other will be retained in study files.

The consent process and decision regarding participation will remain confidential from clinic officials, the study PI, and study co-investigators. Interviews among health care providers will be scheduled to take place in a private setting at a time and date convenient for the provider.

7.5 Confidentiality

All study records will be managed in a secure and confidential fashion. All records will be stored in research office space in locked filing cabinets and access to the records will be restricted to specified study team members. Case report forms and any other study-related documents will be identified using the participant's study number only, with locator information stored separately.

7.6 Data safety and monitoring

There will be no data safety and monitoring board for this study.

8 Project Governance and Management

8.1 Research team

- **Dr. Christopher Hoffmann, MD, MPH, MSc** is a clinician scientist, Associate Professor at Johns Hopkins University. Dr. Hoffmann will provide overall leadership for study implementation.

- **Dr Neil Martinson MBBCh, MPH** is a clinician scientist and Chief Executive Officer of the Perinatal HIV Research Unit. Dr Martinson is the South African Principal Investigator and will oversee implementation and operational aspects of the study and will provide oversight to the South African team.

Study investigators (PI, South African PI, and co-Is) will meet with the PHRU and JHU research managers and the study coordinator on a bi-weekly basis to review study progress. The study team (study nurses, research interviewers, and tracers) will meet weekly to discuss operational aspects of study implementation. Study members from both sites will use the JHU OneDrive, ensuring all members are using the most updated versions of study tools. Any changes to study tools will be first submitted to both Wits and JHU IRBs and communicated to all team members through email upon approval. A study tool adaptation spreadsheet will be created to document each specific change made, date implemented, participants affected, and reason for change. When and where the adaptation was implemented will be reviewed with the field team. There is only one implementation site; the site has standard operating procedures in place to assure that the most current version of protocols and consents are in use. The PI will make 2 visits during study implementation to study sites.

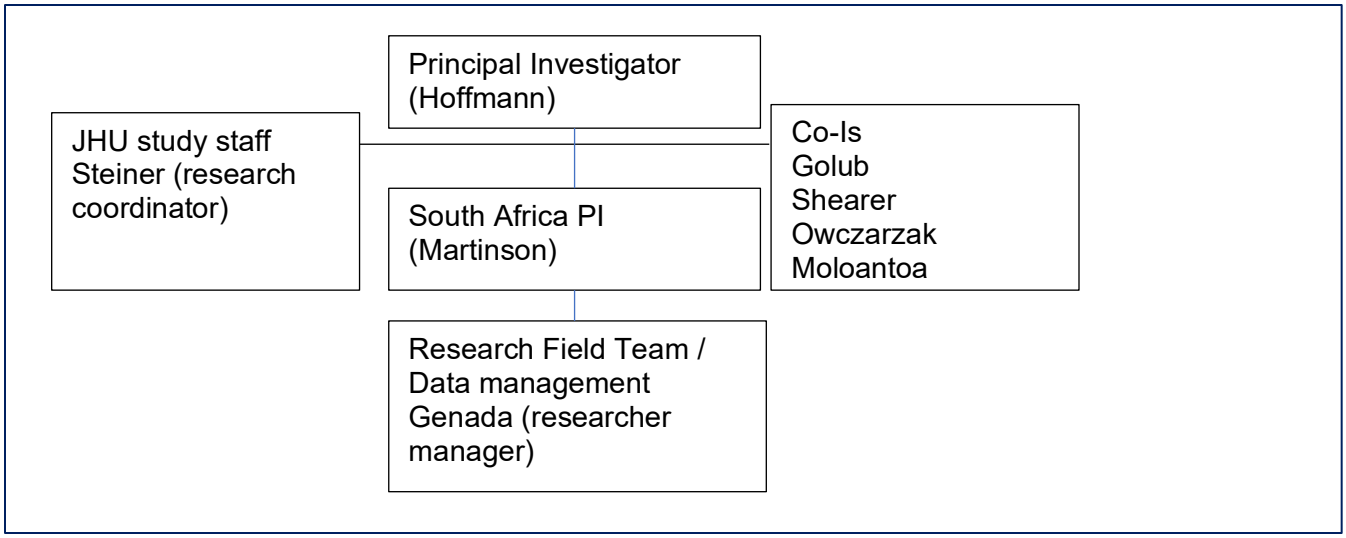

Figure 1: Project Management Structure

8.2 Publication policy

The research findings will be presented first to provincial and national stakeholders and results disseminated by means of local meetings. Results will be written up as one or more articles for submission to a suitable scientific journal.

8.3 Performance monitoring

The principal investigator will complete a monthly progress report that will facilitate monitoring of study progress and keeping the funders informed. These reports will capture vital information, such as IRB timelines, status of protocol development, and any issues/delays that investigators may be experiencing.

9 Participant reimbursement

Participants will not receive payment for participation in the study. Patient articipants will receive R150 for every in-person study contact as compensation for time spent, including initial recruitment during their routine clinic visit and any additional routine follow-up visits required for TB treatment initiation. Healthcare worker participants will receive R80 for participation in in-depth interviews.

10 Funding

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