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Prevent TB: Application of choice architecture to implement TB preventive therapy in South Africa

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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: Clinical guidelines and policies often fail to achieve high levels of delivery of intended clinical interventions. The difference in what we know works and what is actually delivered at the clinic-level to patients, is known as the "science-to-service gap."[1] In the realm of tuberculosis (TB) prevention, this gap is reflected in <20% of TB preventive therapy (TPT) -eligible persons living with HIV (PLWH) being offered or initiated on isoniazid preventive therapy (IPT) in many settings.[2-5] Recent innovation in TPT have brought new pharmacological options allowing for shorter courses, intermittent dosing, or both. For example, a 12-dose once-weekly rifapentine and isoniazid (3HP) regimen has been demonstrated to be effective and well tolerated.[6,7] The science-to-service gap is likely to persist despite improved TPT options.

The overarching goal of this study is to identify a generalizable approach to overcome current barriers to delivery of TPT in order to achieve high levels of TPT delivery during routine care in public clinics. Multiple approaches are in standard use to change prescribing behavior including in service training, audit and feedback, clinical mentoring, the use of clinical decision aids, and "academic detailing."[8,9] Each of these approaches has an evidence-base for improvement in delivery (sometimes limited to a specific setting). However, the overall change is generally modest. For example separate Cochrane Reviews of audit and feedback and academic detailing reported a median increase in service delivery of about 5%.[10,11] To achieve a substantial increase in TPT delivery (from current approximately 20% to 60-80%) will require a fundamental change in the approach to selecting patients for TPT – a redesign of the choice architecture of TPT prescribing.[12]

Aims: To identify a pragmatic approach using choice architecture to increase TPT prescribing to PWH.

Methods: We are proposing a choice architecture that makes prescribing TPT the "default" or standard option and that for TPT not to be prescribed will require a choice by a clinician to "opt-out" of TPT for a specific patient. This will be implemented through combined prescribing stationary or stamps (as appropriate for the context) to make TPT part of ART prescribing or re-prescribing.

We are proposing a cluster randomized design to test the choice architecture approach to increasing delivery of TPT. Clinics will be randomized to one of two strategies: (1) standard implementation and (2) choice architecture default TPT. Because of the clinic-level nature of the implementation strategies, all PLWH receiving care at a clinic will be exposed to the standard implementation or TPT routinization implementation. Clinical process data will be used to assess the effectiveness of each strategy to determine the proportion of PLWH (1) screened for TPT, (2) eligible for TPT, and (3) prescribed TPT.

The primary objective is to test whether this choice architecture approach of a “default” to prescribing TPT substantially increases TPT prescribing. Identifying a pragmatic approach will lead the way for improving TPT prescribing across the study sites. It will furthermore contribute to implementation science at large in describing implementation strategies that may be applied to clinic-level implementation of other innovations.

Significance: TB is the leading cause of death among PWH in South Africa and elsewhere on the continent. TPT is a proven intervention to reduce mortality among PWH but is not widely prescribed. This study seeks to identify an implementation strategy to reach optimal TPT prescribing.

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Contents

Glossary of Terms

AIDS	Acquired Immuno-deficiency Syndrome
ART	Antiretroviral Therapy
CAU	Care as Usual
CBO	Community Based Organization
CCMDD	Central Chronic Medicine Dispensing and Distribution (system or service)
CRF	Case Report Form
DOH	South African Department of Health
HIV	Human Immunodeficiency Virus
LTFU	loss to follow up
NIH	National Institutes of Health
PHC	Primary Health Clinic
PIS	Participant Information Sheet
RCT	Randomized Clinical Trial
SA	South Africa
STI	Sexually Transmitted Illnesses
TB	Tuberculosis

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1 INTRODUCTION

1.1 Background

A.1. Overview. Despite being a preventable and treatable disease, tuberculosis (TB) kills 1.5 million people annually and is the leading cause of death in people with HIV (PWH).[5] TB preventive therapy (TPT) is an evidence-based approach to reducing TB disease and mortality that has been embraced in international and national policies and guidelines. Yet TPT remains woefully under-implemented. We propose to test a choice architecture based strategy to increase initiation of TPT among people with HIV (PWH) in South Africa. Increasing TPT initiation, as called for by global bodies and the South African Department of Health, has the potential to reduce death among PWH receiving antiretroviral therapy (ART).[13,14]

*A.2. HIV associated mortality and TB disease in LMIC.*TB is the leading cause of death due to an infectious agent worldwide.[5,15] Among PWH in low and middle income countries (LMIC), TB represents the leading cause of mortality among PWH.[16] South Africa is particularly affected by the syndemic of HIV and TB with an estimated HIV prevalence in 2017 of 7.2 million and TB incidence of 567/100,000 population with over 60% of TB cases among PWH.[5,17,18] There were an estimated 78,000 deaths from TB in South Africa in 2017; 56,000 of the deaths among PWH.[5] Findings from our group suggest this is likely an underestimate of true TB disease and TB related mortality.[19]

A.3. TB preventive therapy reduces TB disease and mortality. For the past 30 years isoniazid based TPT has been known to reduce the risk of TB among PWH.[20,21] Multiple studies have subsequently confirmed and strengthened this finding. Following cohort studies conducted in South Africa and Brazil by our team that showed marked reductions in TB incidence for PWH, clinical trials of isoniazid preventive therapy have reported up to a 70% reduction in TB incidence among PWH.[22-24] A study conducted in Cote d'Ivoire randomized participants to one of four groups: deferred ART, deferred ART plus TPT using isoniazid preventive therapy (IPT), early ART, and early ART plus IPT. Among over 2000 participants, 175 met the 30 month primary endpoint of mortality, AIDS defining illness, cancer, or invasive bacterial disease. The percentage of participants per group meeting this endpoint was 14% in the deferred ART, 8.8% in the deferred ART plus IPT, 7.4% in the early ART only, and 5.7% in the early ART plus IPT group.[13] Another study from Africa randomized children and adults with CD4 counts <100 cells/mm^3 to ART or ART plus TPT, fluconazole, azithromycin, albendazole, and cotrimoxazole.[25] Among participants in the standard ART arm, 12.2% had died by 24 weeks compared to 8.9% in the enhanced prophylaxis arm (p=0.03).[25] TB disease was reduced from 13% to 8.9% (p=0.007).[26]

A.4. TPT has been embraced by international and national guidelines. In recognition of the role of TPT to reduce TB disease and mortality, the WHO recommended TPT for PWH in 1998.[27] These recommendations have been revised several times since.[28] Multiple national HIV program guidelines and TB control programs also recommend TPT. Current South African Department of Health guidelines recommend TPT to all PWH (without assessment for latent TB infection) stating to "ensure linkage to TPT for all eligible PLHIV" and "initiate IPT at ART initiation for all eligible patients."[29].

A.5. Current delivery of TPT to PWH is anemic. Despite the evidence and guidelines supporting TPT, current delivery of TPT is anemic. Reports from South Africa (and preliminary data by members of this investigative team) have observed between 14% and 35% of eligible patients are prescribed TPT.[2] Other countries in sub-Saharan Africa have similarly low initiation. A study of 102 clinical facilities and 16,433 PWH in Ethiopia reported 3,230 (19.6%) initiated TPT.[3] In Kenya, a report by the national TB program reported only 3.6% of adult ART patients initiated TPT.[4] In Nepal, 32% of eligible patients were prescribed TPT.[30] In 2017, TPT initiation, as reported in the 2018 WHO Global TB Report ranged from 1 to 53% for high burden African countries.[5] South Africa reports higher rates of TPT initiation compared to the rest of the continent, but progress has plateaued and current initiation levels are insufficient for impact.[5,31] Furthermore, our data suggest that the South African national reporting overestimates actual TPT initiation (see Preliminary Studies).

A.6. Patient adherence is good when TPT is prescribed. In contrast to low levels of TPT initiation, a large proportion of patients who receive TPT take it. Among patients who receive TPT in LMICs, adherence ranges from 71-97%.[30,32-35]

A.7. Limited (but real) risks with use of TPT. Increased drug resistance is a potential consequence of inappropriate use of any anti-microbial agent. In practice, isoniazid resistance has not increased in communities with higher TPT use and clinical trials of TPT have not identified an increase in drug resistant TB among participants diagnosed with TB while receiving TPT.[36-38] Best evidence indicates that the risk of substantially increasing drug resistant TB is very low with use of TPT, even when patients with TB disease receive TPT prior to TB diagnosis. Notably, excessive efforts to exclude TB disease can be counterproductive. An intensive screening before TPT study from Botswana compared TB screening with chest X-ray to symptom-only based screening. The strategy using chest X-ray identified more TB cases, but also had 13% more deaths. These deaths were attributed to delays in TPT initiation and lower overall initiation of TPT.[39]

Drug induced liver injury (DILI) is another important, but exaggerated, concern. The risk of fatal DILI from isoniazid TPT is estimated to be between 0.001% and 0.06%. This is similar to the range of DILI risk (fatal and non-fatal) from the commonly prescribed antibiotic amoxicillin-clavulanate.[40] Underlying liver disease, advanced age, and heavy alcohol consumption increase the risk of DILI. In a RCT of TPT in Botswana, there was no difference in side effects (including DILI) between study arms.[39] In another RCT in South Africa, 2.9% of participants in the TPT arm experienced a side effect compared to 1.5% in the placebo arm; none of the side effects were severe and the proportion stopping active drug or placebo due to side effects was similar by study arm.[41] In a cluster randomized trial in South Africa involving 24,221 participants, there were 17 (0.07%) cases of clinical DILI with only one fulfilling criteria for a severe adverse reaction.[42] Importantly, discontinuation of TPT if causing symptomatic DILI generally leads to resolution.[43]

Painful peripheral neuropathy is another potential complication of isoniazid-based TPT. Fortunately, it can be prevented with pyridoxine (vitamin B6) supplementation[44] – as is recommended in South African and WHO guidelines. Notably, both untreated HIV and the ART agent stavudine pose higher risks for peripheral neuropathy than does isoniazid.[45-47] Earlier initiation of ART among PWH, a change in regimens away from stavudine, and inclusion of

pyridoxine with isoniazid have all led to a reduction in peripheral neuropathy in global HIV programs.

A.8.Current barriers to TPT delivery. Key factors leading to low TPT initiation are (1) lack of provider confidence in definitively ruling-out active TB, (2) concerns about increasing drug resistant TB, (3) understanding appropriate screening for TB disease, (4) concerns for DILI, (5) the complexity of prescribing guidelines, (6) misperceptions regarding which patients may benefit, (7) not understanding the benefit of TPT, (8) assumption that patients will not adhere to TPT, and (9) the increased work-load of TPT initiation.[3,34,48-50] All of these factors contribute to the cognitive load of TPT initiation, some also add to the workload. Drug stock-outs in some settings have also posed a barrier to initiation.[3]

A.9. Approaches that have been studied to improve TPT delivery. The majority of studies on TPT have focused on patient adherence to therapy.[51] Two studies from South Africa sought to increase TPT initiation in public clinics. One study sought to integrate HIV and TB services using extra nurses as integration officers.[52] The other sought to make screening for latent TB a routine part of HIV care (although latent TB testing is not currently required in South Africa).[53] Neither study achieved statistical significance in increasing TPT initiation. Single site studies from Papua New Guinea and Nigeria have reported increased TPT initiation through quality improvement approaches and job aids.[8,9] Notably, similar job aids have been implemented in South Africa without resulting in reaching goal TPT initiation [Aurum Institute, personal communication]. An ongoing study in Uganda is testing a co-formulation of isoniazid and cotrimoxazole (a preventive medication for a variety of infections that is more widely prescribed than TPT) [SPIRIT Trial – clinicaltrials.gov]. Another ongoing study is evaluating nurse training and mentoring to increase TPT initiation.[54]

A.10. TPT regimens. The standard TPT regimen is 6 to 12 months of isoniazid (isoniazid preventive therapy; IPT). Two new options for TPT have been developed: (1) three months of weekly rifapentine and isoniazid (3HP) or (2) one month of daily rifapentine and isoniazid (1HP). These two regimens are better tolerated, of shorter duration, and non-inferior to isoniazid only regimens.[6,7] In recognition of potential advantages, the regimen of three months of weekly rifapentine and isoniazid was endorsed by the World Health Organization and the US PEPFAR program in 2019 and the 1HP regimen is expected to be added in the near future. We propose to follow the South African Department of Health TPT regimen that is in use in at the time of the study. Twelve months of daily isoniazid is the current recommendation for PWH in South Africa [DoH Circular, September 2018] but 3HP is expected to be rolled out country-wide in 2020. Thus the flexibility of the proposed implementation strategy is a strength. Should it prove successful in one setting and with one regimen, the approach is highly feasible to adapt to other settings and other TPT regimens.

A.11. HIV and TPT care system in South Africa

South Africa has adopted a model of ART care with ART initiation and maintenance in primary care clinics and community health centers. Within these facilities, nurses are empowered to initiate ART and manage follow-up. In addition to ART, cotrimoxazole and isoniazid TPT are available and can be prescribed by primary care nurses providing HIV care. TB screening is based on asking the WHO four symptom screen (any of cough, fever, night sweats, or weight loss). Patients with a positive symptom screen are meant to receive further evaluation by

sending sputum to a government laboratory for microbiologic analysis using the Cepheid GeneXpert MTB/Rif nucleic acid amplification system. TB disease is usually managed separately from HIV, usually by nurses trained in TB management. Supply chains for ART, isoniazid, cotrimoxazole, and TB medications are reasonably robust, with stock-outs of medications the exception. Prescriptions are written or stamped into the patient's paper chart by the prescribing nurse or doctor. At the time of prescribing, medications are dispensed either at an in-clinic pharmacy or by the provider in the consulting room. Subsequent refills (up to 6 months after original prescription) are filled either at the pharmacy, a "fast-lane" refill station, community distribution, or by a primary care nurse in a consulting room.

A.12. Choice architecture and TPT delivery. Choice architecture is a behavioral economics approach that is used to improve decision making.[12,55] Choice architecture involves deliberate consideration of how options are presented and what follows from each options, including what happens if no active decision is made (sometimes referred to as passive selection or the "default" setting). Choice architecture can reduce time and complexity required for decision making leading to a reduction in the cognitive load.[56] Lower cognitive load can improve decisions; high cognitive load leads to poorer decisions.[56,57]

Examples of choice architecture approaches to improve medical decision making include agreeing to deceased donor organ donation, increasing influenza vaccination, increasing appropriately targeting *Cryptococcus* screening, improved opioid prescribing, and increasing generic medication prescribing.[12,58] In each example, the "default" was altered to enable an individual or provider to select the (usually) most appropriate choice with the least cognitive load. Notably, the alternative decision could be taken as well – allowing for the provider, in shared decision making with the patient, to take the action most appropriate for the individual patient. Making what should usually be the best or most appropriate option the default reduces cognitive load and normalizes the default option (making it okay to do it rather than it being exceptional).

Currently TPT initiation requires an active process to select TPT and a passive (neglecting to consider TPT) process for not initiating. The current active process required for TPT initiation includes at least four steps: (1) consider TPT, (2) evaluate reasons for not initiating, this includes potential concerns for undiagnosed TB and the presence of liver disease, (3) weigh the risks and benefits of TPT, (4) consider patient adherence, and (5) write the TPT prescription. These steps require consideration (cognitive load) and time. Both cognitive load and time compete with other priorities of a complex clinical encounter. As a result, clinicians may "defer" consideration to the "next" visit or turn to rules of thumb to justify deferring or not initiating TPT. Given that the vast majority of ART patients in South Africa would benefit from TPT, the use of choice architecture making TPT the "default" could improve provider decision making and safely increase TPT initiation.

1.2 Study objectives

The overarching goals of this proposal are to test a low-cost and context appropriate approach to translating TPT policy into on-the-ground TPT delivery. We are proposing a cluster-randomized trial (CRT) to measure the effectiveness of a choice architecture-based TPT initiation strategy versus usual prescribing (Figure 1). We anticipate a substantial increase in

TPT initiating, potentially increasing from approximately 35% to 60-80% of ART initiators. This can be achieved through choice architecture and a decrease in cognitive load. We will assess the effectiveness, implementation measures, and patient-level delivery and acceptability to providers.

The primary objectives of this study are:

1. To compare the proportion of patients newly starting ART also initiating TPT within 90 days between the choice architecture and usual prescribing arms
2. To characterize the processes of TPT implementation by study arm including:
    - Provider adoption
    - Fidelity
    - Provider acceptability
    - Intervention maintenance
    - Provider cognitive load of TPT prescribing
    - Clinic workflow integration
3. To describe patient-level characteristics associated with initiating TPT and adhering to TPT

The secondary objectives of this study are:

1. The proportion of patients already on ART initiating TPT within 90 days of a re-prescribing visit
2. The proportion of eligible patients newly starting ART also initiating TPT within 90 days
3. The proportion of eligible patients already on ART initiating TPT within 90 days of a re-prescribing visit
4. The proportion of patients who initiate TPT and discontinue TPT prior to completion

1.3 Significance

TB is the leading cause of death among people with HIV in South Africa and much of the world. TPT is a proven approach to reduce mortality. This study has the potential of identifying an approach to markedly increase TPT prescribing.

2 METHODS

2.1 Study design

We are proposing a clinic-level cluster randomized trial of a strategy to increase the delivery of evidence-based care. Clinics will be randomized to the novel choice architecture strategy arm or usual prescribing arm with analysis based on the clinic-level proportion of TPT initiated. This study will further assess implementation outcomes, the underlying theory of change (the effect of choice architecture on cognitive load), provider experiences with the novel strategy, and patient experiences with TPT by study arm.

2.2 Study setting

The proposed research will be conducted by PHRU in two districts: the Kenneth Kaunda district in the North West Province of South Africa and Mangaung District in the Free State Province. Kenneth Kaunda district has a population of 742,000 [59] and is served by 36 public-sector clinics (primary care clinics and community health centers) providing HIV care (ART, TPT, TB treatment). Mangaung District has a population of 747,431 and is served by 45 public clinics. Both districts have urban, peri-urban, and large rural areas. Both districts are also settings with high HIV and TB prevalence with which the team is very familiar, has a working relationship with the local Department of Health, and has completed prior research on TB and TPT delivery.

2.2.1 Description of the geographical areas of study implementation

The proposed study will be conducted in 36 public clinics that provide antiretroviral therapy (ART). Clinics will be located in rural and peri-urban areas in Kenneth Kaunda especially around Matlosana and JB marks and urban and rural areas of Mangaung, especially around Botshabelo, Bloemfontein and Thaba Nchu.(See clinics)

Kenneth Kaunda District		Mangaung District	
SUBDISTRICTS	**ClinicName**	**SUBDISTRICTS**	**ClinicName**
Matlosana	Marcus Zenzile PHC	Botshabelo	Itumeleng (M)
Matlosana	Kanana PHC	Botshabelo	Dr Pedro (K)
Matlosana	Khuma PHC	Botshabelo	Daniel Ngatane (F)
Matlosana	Tigane CHC	Botshabelo	Maletsatsi Mabaso(B)
Matlosana	RB Nzima Satellite	Botshabelo	TS Mahloko (C)
Matlosana	Stilfontein PHC	Botshabelo	Pule Sefatsa (U)
Matlosana	Delekile Khoza	Thaba Nchu	Mefane
Matlosana	Tsholofelo PHC	Bloemfontein	Opkoms
Matlosana	Empilisweni PHC	Bloemfontein	Thusong
Matlosana	Botshabelo CHC	Botshabelo	Industrial
JB Marks	Top City Clinic	Botshabelo	Potlako Motlohi (L)
Matlosana	Majara Sephapo PHC	Bloemfontein	Mmabana
JB Marks	Steve Tshwete Clinic	Botshabelo	Winnie Mandela (J)
JB Marks	Lesego Clinic	Botshabelo	Herry Gwala(N)
Matlosana	Gateway NM Pretorius PHC	Thaba Nchu	Gaongalelwe
Matlosana	Orkney PHC	Botshabelo	Jazzman Mokhothu (E)
Matlosana	Alabama Clinic	Botshabelo	Molefi Tau (H)
JB Marks	Boiki Thlapi	Thaba Nchu	Thaba Nchu

2.2.2 Rationale for selecting geographical areas of study implementation

We selected these two areas based on a long-standing working relationship between the team and the DoH in these locations and established PHRU research infrastructure in both locations.

2.3 Study Population

The study is a cluster-randomized trial with clinics as units of randomization and the primary outcome measured at the clinic level. The strategy arm seeks to improve delivery of guideline-mandated services to the clinic population. Thus the strategy clinics may have greater prescribing of TPT and anticipated improved health outcomes, but clinic patients will not perceive any differences in care nor will any individual randomization or patient-level consent occur for the primary outcome of the proportion of patients who receive TPT.

2.3.1 Inclusion and exclusion criteria

The unit of analysis and unit of randomization is the clinic. Due to the clinic-level nature of the implementation strategies, all people living with HIV receiving care at a clinic will be exposed to the standard implementation or choice architecture default TPT implementation. All adult (≥18 years old) patients initiating ART or already on ART and coming for ART re-prescribing will be used as denominators for (1) the proportion of ART initiators receiving TPT at the clinic and (2) the proportion of current ART patients receiving TPT at the time of ART re-prescribing.

2.4 Sampling scheme

2.4.1 Clinic selection

Baseline data collection will be completed for a stratified randomization. Key clinic characteristics used for stratification will be measured during a pre-study initiation baseline assessment in the study clinics prior to randomization and will include clinic-level characteristics of patient volume, staffing, and monthly ART initiation.

2.4.2 Clinic level baseline data abstraction

Prior to randomization, data on TPT prescribing, ART initiation, ART maintenance, and clinic staffing will be obtained for the prior 12 months. These data will be abstracted as monthly aggregates from electronic and paper clinic reporting systems (tier.net and clinic registers). No patient level data or identifiers will be abstracted.

2.4.3 Randomization

We will conduct a covariate-constrained randomization to balance the allocation of clinics between the two study arms, ensuring validity of the randomization process (Moulton L.H. Covariate-based constrained randomization of group-randomized trials. Clinical Trials. 2004; 1(3):297-305). Implementation will be staggered over time with 4 clinics (two from each of the arms) entering the study phase every 1-2 months which will provide contemporaneous comparison data (see study implementation timeline). If only a couple of covariates and entry

month /quarter are considered for balance in randomization (i.e. study site and clinic volume of ART patients), a computer-generated stratified randomization sequence based on these covariates will be generated by the study statistician. If multiple covariates are considered for balance, randomization sequences that satisfy the balance and validity criteria across all covariates will be generated and one of those will be randomly selected.

Study implementation timeline

	Y1	Y2Q1	Y2Q2	Y2Q3	Y2Q4	Y3Q1	Y3Q2	Y3Q3	Y3Q4	Y4Q1	Y4Q2	Y4Q3	Y4Q4	Y5
Protocol development	X	X	X											
DSMB meeting		X												
Study initiation activities				X										
Clinic 1-2					X	X	X	X						
Clinic 3-4					X	X	X	X						
Clinic 5-6					X	X	X	X						
Clinic 7-8					X	X	X	X						
Clinic 9-10						X	X	X	X					
Clinic 11-12						X	X	X	X					
Clinic 13-14						X	X	X	X					
Clinic 15-16						X	X	X	X					
Clinic 17-18							X	X	X	X				
Clinic 19-20							X	X	X	X				
Clinic 21-22							X	X	X	X				
Clinic 23-24							X	X	X	X				
Clinic 25-26							X	X	X	X				
Clinic 27-28							X	X	X	X				
Clinic 29-30								X	X	X	X			
Clinic 31-32								X	X	X	X			
Clinic 33-34								X	X	X	X			
Clinic 35-36								X	X	X	X			
Data analysis and write-up											X	X	X	X

Sample Size Justification. The primary outcome is the proportion of adult patients newly initiating ART who are also initiated on TPT. We hypothesize that 35% of eligible patients in the standard strategy approach will receive TPT as found in the TEKO study completed by Dr Golub and Martinson[53] while the proposed opt-out intervention will increase this proportion to 50-60% of eligible patients. Historical data indicate that the annual number of eligible patients (i.e. initiating ART) will be 200 per clinic.[53] Table 1 illustrates different scenarios of the coefficient of variation (CV) which was found to be between 0.4 and 0.5 in prior work that involved only 14 clinics by the study team in one of the proposed study districts. For this trial, a larger number of clinics and stratification by important baseline covariates is expected to reduce the CV. A total of 36 clinics (18 per arm) is feasible within the available resources and it will enable us to detect a meaningful difference of 20 percentage points with 80% power at a 5% level of significance. We will stratify the randomization by the clinics' annual visits and other available covariates (TPT prescribing, ART initiation, ART maintenance, and clinic staffing for the prior 12 months) in order to control the between-clinic coefficient of variation and to improve the efficiency of the estimates.

Table 1. Number of clinics required for 80% power to detect a difference in proportion initiating ART and TPT between the two study arms

Proportion initiating TPT in standard approach	Proportion initiating TPT in opt-out arm	Coefficient of variation	Required Number of clusters per arm
35	50	0.3	14
35	55	0.3	9
35	60	0.3	7
35	50	0.4	23
35	55	0.4	15
35	60	0.4	11
35	50	0.5	35
35	55	0.5	23
35	60	0.5	17

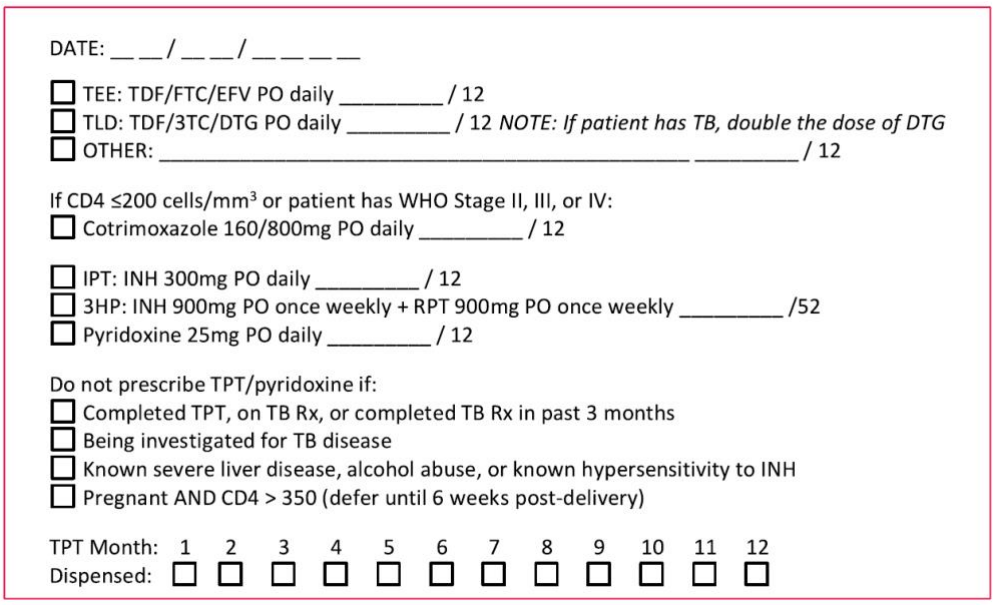
2.4.4 Choice architecture arm

In the choice architecture implementation strategy, all opt-out clinic providers and pharmacists will be trained on the approach. The fundamental tenant of this approach is that TPT will be prescribed with any ART initiation and any ART re-prescribing for 3-12 months of TPT (adherent to current guidelines) if TPT has not been previously prescribed or if there is uncertainty regarding previous prescribing. This will be facilitated by co-prescribing ART and TPT. That is when ART is being prescribed, TPT is meant to be prescribed at the same time of the clinic visit.

The simultaneous prescribing will be facilitated through the introduction of an ink stamp or pre-printed sticker to use for quick entry of the ART prescription along with TPT and cotrimoxazole (Figure). This stamp/sticker will be available in the consulting rooms and will be pre-stamped/applied by file clerks to files when retrieved. The stamp/sticker for ART prescription, the prescription for TPT and for cotrimoxazole will be "automatically" included. Active canceling of these prescriptions (and indicating the reasons) will be needed to *not* have TPT dispensed.

The stamp/sticker design and content will be finalized in consultation with the clinicians and the PHC nurses working in those districts to ensure that it is aligned with the latest guidelines and stationery being utilized in the health facilities. If necessary, the design and size might vary between the two provinces.

Figure 1. TPT choice architecture aid


DATE: __ __ / __ __ / __ __ __ __

☐ TEE: TDF/FTC/EFV PO daily _____ / 12
☐ TLD: TDF/3TC/DTG PO daily _____ / 12 *NOTE: If patient has TB, double the dose of DTG*
☐ OTHER: _____ _____ / 12

If CD4 ≤200 cells/mm³ or patient has WHO Stage II, III, or IV:
☐ Cotrimoxazole 160/800mg PO daily _____ / 12

☐ IPT: INH 300mg PO daily _____ / 12
☐ 3HP: INH 900mg PO once weekly + RPT 900mg PO once weekly _____ /52
☐ Pyridoxine 25mg PO daily _____ / 12

Do not prescribe TPT/pyridoxine if:
☐ Completed TPT, on TB Rx, or completed TB Rx in past 3 months
☐ Being investigated for TB disease
☐ Known severe liver disease, alcohol abuse, or known hypersensitivity to INH
☐ Pregnant AND CD4 > 350 (defer until 6 weeks post-delivery)

TPT Month: 1 2 3 4 5 6 7 8 9 10 11 12
Dispensed: ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

2.4.5 Standard of care arm

The standard TPT implementation is for a clinician to screen for TB and to consider TPT for those who do not have "presumptive TB". Clinicians in the study district (and most districts in South Africa) have received training and job aids to assist in appropriate application of the TPT initiation algorithm. Prescribing for TPT and ART is done by writing, by hand, the prescription in the patient's paper file. As part of this study, all study clinic providers will have access to standard Department of Health printed material and clinical training.

2.5 Study outcomes

2.5.1 CRT primary and secondary effectiveness outcomes

The primary outcome is the proportion of ART initiators also initiating TPT. This includes patients who are ART naïve and those re-initiating ART after a lapse in therapy. Secondary outcomes are the proportion of already on-ART patients initiated on TPT, the proportion of

eligible patients initiated on TPT (with ART initiators and re-prescribing reported separately), and the proportion of patients initiated on TPT with a subsequent discontinuation prior to completing the course of therapy. Adjustment for sex and age strata, as a clinic proportion, will be conducted as a secondary analysis. TPT initiation will be ascertained from all available data sources in the clinics, including but not limited to paper files, clinic registers, pharmacy records, DHIS2, and the electronic HIV health information reporting system (tier.net). Similarly the total number of ART initiations and ART re-prescription, and age and sex distribution will be ascertained from the same data sources. Analytic approaches for Aim 1 are described in Table 2. A detailed statistical analysis approach will be contained in the study Statistical Analysis Plan.

Table 2. Aim 1 outcomes & analysis approach

	Outcomes	**Data source**	**Statistical Test**
Primary	Proportion of ART initiators initiated on TPT	Paper files, clinic registers, pharmacy records, DHIS2, Tier.Net	The primary analysis will apply the unpaired t-test of the cluster-level proportions, keeping with the randomized nature of the design. Residual confounding by stratification variables used in the randomization, entry month /quarter and other clinic characteristics will be adjusted for using a log-binomal regression with robust variance estimation to account for clustering by clinic. [60]
Secondary	Proportion of already on ART patients initiated on TPT	Paper files, clinic registers, pharmacy records, DHIS2, Tier.Net	
Secondary	Proportion of TPT "eligible" patients initiated on TPT (ART initiators and ART re-prescribing, separately)	Paper files, clinic registers, pharmacy records, DHIS2, Tier.Net	
Secondary	Proportion of patients started on TPT with subsequent discontinuation	Paper files, clinic registers, pharmacy records, DHIS2, Tier.Net to identify noted stopping for possible adverse effect	

2.5.2 Assessment of clinic implementation of choice architecture

Implementation measures: Adoption will be assessed as the proportion of visits in which the choice architecture strategy was used (as measured by use of the pre-printed/stamped prescription), regardless of the clinician's initiation decision. Fidelity will be assessed through the proportion of visits for which the clinician opts not to prescribe and has indicated a reason for not initiating. Maintenance will be assessed by evaluating the adoption of the choice architecture approach by month from start to end of the study implementation in each choice architecture strategy clinic. The twelve month implementation period is sufficient to observe *desensitization* toward a strategy among providers and thus assess maintanence.[61] A decline in use of the choice architecture strategy along with a decline in TPT initiation will suggest a potential problem with maintaining the strategy over time.

Population: All study clinics and all ART prescribing encounters at these clinics will be used to assess the implementation measures.

Analysis: We will use descriptive statistics to characterize each of the implementation outcomes. Adjusted chi-squared statistics (Reed 2004; Jeph Herrin, 2002. "CLTEST: Stata modules for performing cluster-adjusted chi-square and t-tests," Statistical Software Components S424901, Boston College Department of Economics, revised 03 Feb 2012.) that account for clinic clustering will be used to compare proportions by and by population of interest.

Acceptability evaluation: Acceptability will be assessed among providers in the choice architecture strategy arm using a researcher administered and self-completed (mixed) acceptability questionnaire. The questionnaire will be based on the theoretical framework of acceptability developed by Sekhon et al.[62] This framework has seven core constructs: attitude (how an individual feels about the strategy), burden (effort required for the strategy), ethics (concurrence with value system), coherence (how well the strategy is understood), opportunity costs, perceived effectiveness, and self-efficacy (confidence in using the strategy). The acceptability scores will be interpreted in the context of the study efficacy results with a general threshold of the majority of participants scoring the constructs as acceptable (responses on Likert scale). Findings from the acceptability questionnaire will be further explored through in-depth interviews in a sequential explanatory mixed methods approach (described as follows).

Population: We will invite all HIV care providers at the study clinics, who have spent 3 or more months at the study clinic, to complete the acceptability assessment.

Analysis: Acceptability will be scored as a mean (if normally distributed, otherwise median) per domain with 95% confidence intervals (if normally distributed, otherwise inter-quartile range). Hypothesis testing will be used to compare the score to a neutral (3 on a 5-point Likert scale) response. Scores will be interpreted with a general threshold for acceptability if mean or median score favors acceptability.

Cognitive Load Assessment.

We will use instruments self-completed by providers with support from the study staff to assess cognitive load. Cognitive load theory was developed in educational psychology to explain learning of complex tasks[63] and has been extended to understand decision making in medical care. Several instruments have been developed for measuring cognitive load. The Paas scale,[64] is among the earliest and most heavily used, including in healthcare applications.

Population for cognitive load assessment. All health care workers who prescribe ART at each of the study facilities (3-4 providers per facility) will be invited to complete these instruments through self-administration with support from the study staff (to reduce social desirability bias). We will ask health care workers to complete these instruments during breaks during an ART prescribing day. We anticipate approximately three or four healthcare workers per facility, for a minimum sample size of approximately 60-70 providers per arm . We follow a conservative approach and assume that 50% of the providers in the standard arm will express moderate or very high cognitive load in a typical assessment question. If we assume a design effect of 1.5, the effective sample size ~80 overall would enable us to estimate the overall prevalence with an 11 point margin of error (95% CI width of 22); and it would provide 82% power to detect a

reduction of 20 percentage points in the more strategy arm (n=40 per arm). A higher design effect of 2 would provide 69% power to detect this difference.

Procedures for measuring cognitive load. We propose to include three separate brief scales of cognitive load and task load: the Paas scale, the Klepsch scale, and the NASA Task Load Index. We have selected these instruments because they each measure slightly different aspects of cognitive load and all three have been used to assess decision making or task performance in medical settings.[63-66] The Paas scale uses a Likert scale with a single question, the Klepsch scale uses 7 items, each with a 5-point Likert scale; two of the items map to intrinsic cognitive load, two to extraneous cognitive load, and three to germane cognitive load. The NASA Task Load Index (TLX) has six questions each rated with a scale and is focused on task complexity and difficulty in completing (Appendix B).[65] We will calculate a composite score for each instrument to have three cognitive load scores.

Cognitive load analysis: We will assess each scale independently and then assess inter-scale consistency across scales (Cronbach's alpha). The analysis will be in two parts. For each assessment question / subscale rating, we will compare the proportions of participants who report moderate to high load between the two study arms using log-binomial regression with robust variance to account for within-clinic clustering, and the resultant p-values will be adjusted for multiple testing to control the Type-1 error rates due multiple testing. We will then use exploratory factor analysis to generate cognitive load score for each scale, and this load score will be compared between the two study arms using either the Kruskal-Wallis test, a non-parametric method, or t-test if the results are normally distributed.[67]

Workflow integration and congruence assessment: We will conduct semi-structured interviews among providers. We will use an interview guide developed based on the constructs of Normalization Process Theory.[68] These are interactional workability, relational integration, skill-set workability, and contextual integration and acceptability constructs. The interview guide will be further informed by findings from the process measures, acceptability questionnaire, and cognitive load measures. Interviews will be conducted in a private setting in the language of choice of the provider (generally English) and digitally audio-recorded. Audio-recordings will be transcribed and translated (as needed).

Population: We will seek to recruit 15-20 providers from each of the choice architecture and usual prescribing arms (total 30-40). We will seek to maximize diversity and representativeness among levels of providers (primary care nurses and doctors) through purposively selecting a range of ages, men and women, and duration of practice. A randomization scheme stratified by the above characteristics will be generated among all prescribers present at the 9-18 month of study implementation time, who have been providing ART care for at least 2 months at the study clinic. A random selection of providers, by random number generation, will then be invited to participate in the structured interviews.

Analysis: Transcripts of audio-recordings will be uploaded into MaxQDA 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.[69,70] 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 Owczarzak and will be assisted by the experienced qualitative PHRU team. Qualitative analysis will proceed by first exploring broad patterns and experiences of clinicians, and then assessing possible similarities and differences in experiences between providers (including different ages, sex, and level of training.).

2.5.3 Patient initiation and completion of TPT

Aim: to evaluate factors associated with TPT initiation and completion. These factors will include sex, advanced HIV (CD4 <100 cells/mm^3) compared to less advanced HIV, younger (aged <35 years old) compared to older patients; ART initiation and regimen; economic factors (e.g. employment) and clinical factors (e.g. close contact TB history). A subset of the enrolled participants will be invited for in-depth interviews to assess experience with TPT .

Setting & Population. ART initiators and established ART patients will be

a) Recruited by study staff using a convenience sampling method inboth choice architecture and usual prescribing clinics. Study staff will inform eligible patients about the study as they are waiting for their consultation.
b) Clinic staff will refer individuals for further information from the study team and enrollment.

Potential partcipants identified through this process will be provided study information and undergo the consent process in a private area in the clinic. The consent process and the subsequent participant interview will be conducted in a private area to assure confidentiality. TB and HIV will not appear in any prominent places on any of the documents and all study forms (aside from the informed consent document) will be identified by study identification number.

Between 3 and 12 months from the time a patient could have initiated and may still be receiving TPT (3-9 months after ART initiation or 3-12 months after a re-prescribing visit) patients will be invited to participate. Consent will be sought for both clinical record abstraction and a structured interview.

We propose to enroll an equal number (n=20) of participants per clinic in order to reduce between cluster size variability, for a total of approximately 720. Assuming a null prevalence of 35% to 50% initiation for a given group defined by a category within any of the factors being evaluated (e.g. males vs females), and moderate to high design effects due to similarity in the intiation rates within clinics, this sample size will provide more than 80% power to detect a 20 percentage point difference in the outcome (Table 3). We anticipate >3,600 ART initiators at clinics in each study arm during the duration of study implementation making the proposed sample size highly feasible to recruit.

Table 3**. Power calculation for patient initiation and completion**

Null prevalence of TPT initiation	Design effect	Detectable difference	Power
0.35	2	0.15	0.82
0.35	2	0.2	0.97

0.35	3	0.15	0.65
0.35	3	0.2	0.89
0.50	2	0.15	0.82
0.50	2	0.2	0.97
0.50	3	0.15	0.65
0.50	3	0.2	0.89

Procedures

Clinical assessment: Clinical records (paper and electronic records) for participants in this aim will be abstracted for key clinical characteristics including: ART initiation and regimen, CD4 count results, HIV viral load results, hepatitis B test results, COVID-19 test results, clinical documentation of prior TB, prior TPT, alcohol use, liver disease, TPT initiation and medication pickups, TB screening, TB diagnoses after TPT initiation, medication discontinuations with reason when noted (e.g. suspected side effects), and documented potential side effects. This chart abstraction will occur as a single cross-sectional assessment.

Structured interview: The structured quantitative patient interview will include closed-ended questions regarding demographics, food security, income, employment, prior TB history, close contact TB history, prior ART history, prior TPT, COVID-19 history, current smoking status and smoking history, current alcohol use, current known liver disease, awareness of TPT, receipt of TPT, adherence to TPT if prescribed, and experience with TPT if prescribed (e.g. suspected side effects).

In depth interview: A subset of 30-45 patients among the 720 recruited for TPT assessment will be invited for participation in in depth interviews to explore understanding and experience with TPT.

Analysis. Quantitative data from the clinical abstraction and structured interviews will be combined for analysis. Descriptive statistics will be used to characterize the population and attributes of patients in each of three outcome categories: participants who initiated and completed TPT, those who were initiated on but did not complete TPT, and those not initiated on TPT. Log-binomial regression with robust standard errors to adjust for clustering will be used to assess differences in TPT receipt by each factor, adjusting for the main effect of study arm. We will also conduct a similar analysis for factors associated with completing TPT. The factors to be evaluated will include advanced HIV (CD4 <100 cells/mm^3) compared to less advanced HIV, sex, and younger (aged <35 years old) compared to older patients. We will evaluate whether study arm acts as a mediator (rather than a confounder) between these factors and initiation/completion of TPT using simple generalized structural equation models. Descriptive statistics will be used to characterize any reported side effects or other challenges with TPT. Mixed effects logistic or log-binomial regression (depending on prevalence of side effects) will be used to compare self-reported and clinical record documented side effects by study arm and other key characteristics, including age group and sex.

2.5.4 TB Patient Care

Aim: to understand which services patients are offered during their TB treatment in both usual prescribing and choice architecture clinics.

Setting & Population. In order to ensure accuracy of the information collected, a study team member will request to speak with a provider that has been providing TB care to patients for >=2 months at the study clinic. One or more TB healthcare providers will be selected to review the clinic TB stationary with study staff.

Procedures

Chart Review: People with TB are often co-afflicted with other health and socio-ecominc conditions that can potentially be screened for and treated/addressed during TB treatment. These co-morbidities include tobacco use, alcohol abuse, mental health issues, pre-diabetes or diabetes, hypertension, food insecurity, and lung impairment. We plan to review current screening and care practices at the study clinics in the North West province to determine what services are currently available for people with TB. We will review current forms used at TB screening and diagnosis with one or more TB care providers, ask what services are provided in the clinic, and which services are referred out of the clinic. The proposed activity is expected to take less than 15 minutes in each clinic. No identifying information will be collected from the health care providers, no preferences or opinions will be collected from the providers, and data will be entered into a de-identified REDCap database.

3 Analysis: Descriptive statistics will be generated to describe availability and utilization of services for TB patients.Data Management

Data will be collected to review study associated outcomes in order to evaluate the extent to which the case management goals and objectives are being met. To achieve this, data will be collected in the pre- and intervention study periods. In addition to this, data will also be collected to assess actual programme performance against planned activities.

3.1 Data collection tools

Table 4. List of data collection tools and intended use

Name of tool	Purpose	Schedule	Study arm
Clinic baseline ART and TPT characteristics & clinic characteristics (CL001)	To describe record key clinic characteristics and ART initiation, ART maintenance, and TPT prescribing over the preceding 12 months	Pre-randomization	Both
Clinic baseline ART and TPT characteristics & clinic characteristics (CL002)	To describe record key clinic characteristics and ART initiation, ART maintenance, and TPT prescribing over the current 12 months of study	Post Randomization	Both
TPT001	To abstract ART prescribing (new patients), ART re-prescribing (current patients), TPT prescribing,	Monthly	Both

	and adoption of TPT assessment (choice architecture clinics only)		
Acceptability to health care workers (F002)	Quantitative interview of acceptability domains	9-18 months after study initiation	Choice Architecture clinics only Intervention only
Cognitive load for health care workers (F003)	Measures of cognitive load to assess the overall cognitive load of clinical decision making and the specific burden of TPT prescribing	9-18 months after study initiation	Both
Patient TPT use (PT001)	Baseline demographic and health data collected from subset of patients	3-12 months after TPT initiation (or potential TPT initiation)	Subset of 720 participants drawn from both arms
Patient TPT clinical record review (PT002)	Clinical data collected related to time of TPT initiation and 12 month follow-up	12 months after TPT initiation (or potential TPT initiation)	Subset of 720 participants drawn from both arms
Health care worker interview guide (IG001)	Interview guide for assessing workflow integration of choice architecture TPT	9-18 months after study initiation	Both
Patient interview guide (IG002)	Interview guide for patient-level factors related to TPT.	3-12 months after TPT initiation (or potential TPT initiation)	Both
TB Patient Care (PC001)	To describe the services offered to patients during their TB treatment	1-12 months after study initiation	Both

3.2 Database

3.2.1 Structure of the database

This study will rely on two databases within the secure web-based REDCap™ (Research Electronic Data Capture) system. One will be used to capture participant-level demographic and clinical data obtained from clinical record abstraction and structured interviews (participant database). The other database will be a clinic-level database used for collection of monthly data points (clinic database). The Redcap database 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 sourcesWe will develop a separate database

form within REDCap for each paper 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 the paper CRFs.
Data entry validation and automatic range checks will be incorporated in most data fields to reduce data entry errors. In addition, a data monitor will compare approximately 10% of CRFs with data within the database. This will help to identify systematic errors. Such problems may lead to a review of a larger proportion of CRFs. In addition, bi-weekly electronic checks for inconsistencies within and across forms will be performed followed by CRF review of any data queries that are generated.

3.2.2 Database access

Access to the database (data entry, reporting, and extraction) is controlled by the Data Manager, Study Manager, 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.

3.2.3 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.

3.2.4 Data security

All paper study records (e.g. consent forms, screening logs) will be kept in a secure location accessible only to authorized study staff, investigators, and monitors. All CRFs will be identified with study ID numbers and will not contain personal identifiers.

3.2.5 Study limitations

The proposed implementation research has the following limitations:

- Participant self-report regarding lapses in medications may introduce bias as participants may favour the most socially acceptable responses. Verification of self-reported adherence using clinic records will be conducted, where possible, for all participants.
- Observation of providers in the intervention clinics may result in modified or improved TPT prescribing because of the fact that they are being studied
- Patient loss to follow-up may hinder the study team's ability to assess the outcomes of TPT adherence and TPT discontinuation.
- The study team will be relying on routine clinical records to determine patient eligibility for TPT and the ability of the team to determine TPT eligibility may be hampered by incomplete documentation of patient eligibility. This may be a larger issue in the standard of care arm.

4 Appropriate care in response to study-specific findings

Aggregate data will be collected for the primary CRT outcomes. No specific patient level care will be able to be guided from these data. Clinical data will be collected among a subset of 720 individually enrolled participants. However, these clinical data will be collected retrospectively. As a result, no specific response to care will be possible. Any increase in reported side effects in the intervention arm will be reported to the DSMB for review and guidance on course of action.

5 Protection of human participants

5.1 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 University of the Witwatersrand Human Research Ethics Committee, North West and Free State Provinces, and the Johns Hopkins University IRB.

5.2 Risks and benefits

- The primary goal of this study is to improve appropriate prescribing of TPT. The risks overall are no greater than risks from normal medical care.
- Among patient participants recruited for additional evaluation 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 and quantitative surveys 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 other Department of Health personnel.

1. **No excessive inducements for participation.**

Participants will not receive specific remuneration for overall study participation. Any patient travel will be compensated for in depth interviews or other specific data collection activities at a value of R150.

2. **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 spoken in the North West and Free State provinces.
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 clinicians 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 on 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.

3. Health care worker participation

Health service staff involved in TPT prescribing will be recruited for participation. Selected staff members will be invited by a study team member to participate. Study information will be provided to the potential staff participant. Staff willing to participate will be asked to sign a written informed consent document in duplicate. One copy will be provided to the staff member 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 staff participants will be scheduled to take place in a private setting at a later time and date.

5.3 Clinical trials registration

The study will be registered with clinicaltrials.gov. Key study information and results will have open-access availability on the clinicaltrials.gov website. This is in accord with funder (NIH) regulations.

5.4 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 case management documents will be identified using the participant's study number only, with locator information stored separately.

5.5 Data safety and monitoring

A data safety and monitoring board will be established to review the protocol and monitoring plan prior to commencement of enrollment into the CRT and meet virtually prior to commencing enrollment and then every 6 months to review CRT progress, enrollment and outcomes data, and any potential adverse outcomes. The meetings will review safety to suggest procedural changes and study modifications. The DSMB will include 3-5 members including individuals with experience with HIV care, clinical outcomes research, clinical trials, and good clinical practice.

6 Project Governance and Management

6.1 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 Limakatso Lebina MBChB, MPH** is a clinician scientist and Director at the Perinatal HIV Research Unit. Dr Lebina is the South African PI and will oversee the implementation and operational aspects of the study.
- **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 Co-Investigator and will provide oversight to the South African team.

The study team (PI, South African PI, and co-Is) will meet biweekly to review study progress. The team will meet weekly to discuss operational aspects of the study implementation. Dr Owczarzak will meet as needed for qualitative analysis components. The PI will make 3 – 4 visits annually to study sites.

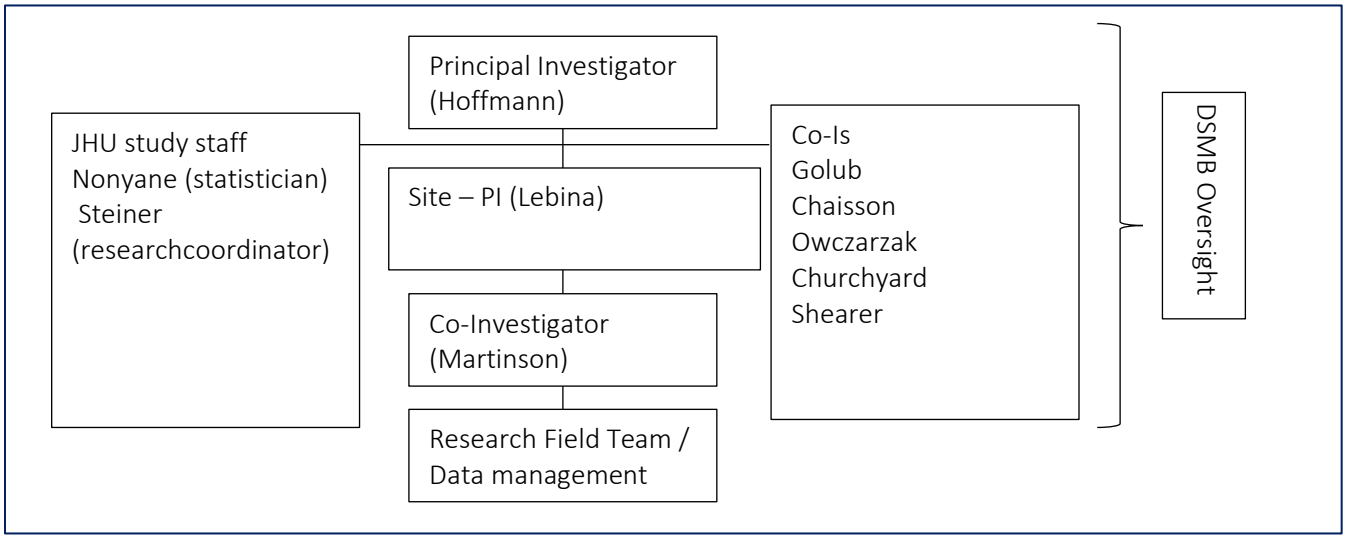


Figure 2: Project Management Structure

6.2 Publication policy

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

6.3 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, enrolment figures, and any issues/delays that the PI may be experiencing.

7 Participant reimbursement

Participants will not receive payment for participation in the study. Participants will receive reimbursements for time and or travel for in-depth interviews and other data collection requiring travel.

8 Funding

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