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

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Fedisa TB:

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

STATISTICAL ANALYSIS PLAN

Version 1

Principal Investigator: Christopher Hoffman

South African Principal Investigator: Limakatso Lebina

Prepared by: Christopher Hoffmann, Kate Shearer, and Aletta Nonyane

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1 INTRODUCTON

The present document comprises the Statistical Analysis Plan (SAP) for the Fedisa TB study, designed to demonstrate effectiveness of a choice architecture approach to default TB preventive therapy (TPT) prescribing for people living with HIV (PLHIV) in South Africa. Additionally, this study will characterize the process of TPT implementation, assessing provider adoption, fidelity, acceptability, intervention maintenance, provider cognitive load, and clinic workflow integration.

1.1 Scoping statement

The SAP contains:

- The details of the planned statistical analyses associated with a study so that the analyses are planned with the desired work product(s) in mind and can be conducted in a consistent, repeatable manner.
- The SAP may include example tables, figures and listings.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study objectives

Primary objectives

- To compare the proportion of patients newly starting ART also initiating TPT between the choice architecture and usual prescribing arms
- 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
- To describe patient-level characteristics associated with initiating TPT and adhering to TPT

Secondary objectives

- The proportion of patients already on ART initiating TPT
- The proportion of eligible patients newly starting ART also initiating TPT
- The proportion of eligible patients already on ART (prior to study start) initiating TPT
- The proportion of patients who initiate TPT and discontinue TPT prior to completion

2.2 Trial design

This is a cluster randomized trial designed to test the effectiveness of a choice architecture approach to default TPT prescribing. We will randomize 36 clinics located in North West and Free State Provinces of South Africa to either routine or default prescribing of TPT.

2.3 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 while the proposed opt-out intervention will increase this proportion to 55-65% of eligible patients. Historical data indicate that the annual number of eligible patients (i.e. initiating ART) will be 200 per clinic. 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 district. 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 initiation

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 Clinic 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. Implementation will be staggered over time with 4 clinics (two from each of the intervention arms) entering the study phase every month, which will provide contemporaneous comparison data (see study implementation timeline). If only a couple of covariates are considered for balance in randomization (i.e. study site and clinic volumes 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.

3 GENERAL ANALYSIS DEFINITIONS

3.1 Study period

Implementation at selected clinics is expected to start in the first half of 2020 and will be completed in late 2021 (see table 2).

Table 2: Study implementation timeline

	Y1Q1	Y1Q2	Y1Q3	Y1Q4	Y2Q1	Y2Q2	Y2Q3	Y2Q4	Y3Q1	Y3Q2	Y3Q3	Y3Q4	Y4Q1	Y4Q2	Y4Q3	Y4Q4	Y5
Protocol development	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

Table 3: Schedule of case report forms

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
ART initiation & ART re-scripting (RX001)	To abstract daily clinic totals of ART prescribing (new patients) and ART re-prescribing (current patients) and TPT prescribing.	Monthly	Both
TPT early discontinuation (RX002)	To record any notes reasons for TPT discontinuation in the TPT register	Monthly	Both
Adoption of TPT assessment (F001)	To document use or non-use of the streamlined TPT approach.	Monthly	Choice architecture
Acceptability to health care workers (F002)	Quantitative interview of acceptability domains	9-12 months after study initiation	Both
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	9-12 months after study initiation	Both
Patient TPT use (PT001)	Baseline demographic and health data collected from subset of patients	3-9 months after TPT initiation	Subset of 600 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	Subset of 600 participants drawn from both arms
Health care worker interview guide (IG001)	Interview guide for assessing workflow integration of choice architecture TPT	9-12 months after study initiation	Both
Patient interview guide (IG002)	Interview guide for patient-level factors related to TPT.	3-9 months after TPT initiation	Both

3.2 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.

Intention to treat: The primary analysis will be based on an intention to treat with all clinics analysed by arm randomized to.

3.3 Subgroup definitions

Sub-group analyses using aggregate data will take place for the following variables;

- ART status (new vs established patients)
- Sex
- TPT eligibility status, if available

4 STUDY PARTICIPANTS

4.1 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.

5 EFFECTIVENESS EVALUATION

5.1 Definitions

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 clinic TPT registers 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 clinic ART registers and the tier.net system. Total numbers will be abstracted from the clinics without patient level details. Analytic approaches for Aim 1 are described in below.

Table 4: Aim 1 outcomes & analysis approach

	Outcomes	Data source	Statistical Test
Primary	Proportion of ART initiators initiated on TPT	TPT initiation register, daily ART initiators, TB treatment registers	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 and other clinic characteristics will be adjusted for using a log-binomial regression with robust variance estimation to account for clustering by clinic..[60]
Secondary	Proportion of already on ART patients initiated on TPT	TPT initiation register, daily ART initiators, TB treatment registers	
Secondary	Proportion of TPT "eligible" patients initiated on TPT (ART initiators and ART re-prescribing, separately)	TPT initiation register, daily ART initiators, TB treatment register.	
Secondary	Proportion of patients started on TPT with subsequent discontinuation	TPT register review. to identify noted stopping for possible adverse effect	

6 IMPLEMENTATION ASESSMENTS

Implementation outcomes are defined as follows:

Table 5: Implementation outcomes

Implementation outcomes	Adoption of intervention
	Fidelity
	Maintenance
	Acceptability of intervention
	Cognitive load assessment
	Workflow integration and congruence assessment

Table 6: Measures and analysis for adoption, acceptability, cognitive load, and workflow integration and congruence

Assessment	Assessment methods	Timing	Statistical test
Adoption			
Adoption	Proportion of visits in which the choice architecture strategy was used, as measured by the use of the pre-printed/stamped prescription, regardless of the clinician's initiation decision	End of study implementation	Descriptive statistics will characterize each of the implementation outcomes by study arm (as appropriate). Adjusted chi-squared statistics that account for clinic clustering will be used to compare proportions by study arm (when
Fidelity	Proportion of visits for which the clinician opts not to prescribe and has indicated a reason for not initiating	End of study implementation	

Maintenance	Adoption of the choice architecture approach by month from start to end of study implementation in each choice architecture strategy clinic	End of study implementation, presented monthly	measured in each study arm) and by population of interest within a study arm.
Acceptability			
Acceptability	Assessed using a researcher-administered acceptability questionnaire based on the Sekhon framework of acceptability using 7 core constructs	Up to 1 year after study implementation	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 (4 on a 7-point Likert scale) response. Scores will be interpreted with a general threshold for acceptability if mean or median score favors acceptability.
Cognitive Load			
Paas Scale	Likert scale with a single question	9-12 months after study implementation	Each scale will be assessed independently and then inter-scale consistency across scales will be assessed (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.
Klepsch Scale	7 items, each with a 7-point Likert scale - 2 map to intrinsic cognitive load - 2 map to extraneous cognitive load - 3 map to germane cognitive load		
NASA Task Load Index	6 questions each rated with a scale focused on task complexity and difficulty in completing		

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. 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 9-12 month of study implementation time. 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).

7 ADVERSE EVENTS

Adverse outcomes will be primarily identified during data collection activities at clinics, through clinical record review, and patient interviews. However, as this study is testing an implementation strategy rather than either a chemical or behavioral therapy intervention, serious adverse events (SAEs) are not anticipated.