INNOVATIVE CONTACT TRACING STRATEGIES FOR DETECTING TB IN MOBILE RURAL AND URBAN SOUTH AFRICAN POPULATIONS

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Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)
- ICH GCP E6
- Completion of Human Subjects Protection Training
- NIH Clinical Terms of Award

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.
http://www.fda.gov/cder/guidance/959fnl.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html
http://cme.cancer.gov/c01/

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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ACF	Active Case Finding
AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DHHS	United States Department of Health and Homeland Security
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NICD	National Institute For Communicable Diseases
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PI	Principal Investigator
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TB	Tuberculosis
WHO	World Health Organization

Title: Innovative contact tracing strategies for detecting TB in mobile rural and urban South African populations

Population: 4,800 male and female newly diagnosed TB cases age 0-99 years and their estimated 9,600 household contacts in Limpopo, North West and Gauteng provinces, South Africa

Number of Sites: See Section 1/Appendix

Study Duration: 5 years total (2.5 years of enrollment)

Subject Duration: Single visit (30-45 minutes)

Objectives:

Primary:
To measure the comparative effectiveness of two novel household-based TB contact investigation strategies: 1) tracing on holidays in rural areas; 2) tracing on evenings and weekends in urban areas versus tracing during working hours (standard household contact tracing).

Secondary:
To compare the implementation, effectiveness, cost-effectiveness and potential impact of rural holiday and urban off-peak contact investigation against standard contact investigation in South Africa

a) Assess the effectiveness of each novel strategy compared to standard contact tracing by setting (rural versus urban).
b) Examine metrics of acceptability, feasibility, fidelity and sustainability for each novel strategy relative to standard contact investigation.
c) Measure costs of each intervention and estimate cost-effectiveness (incremental cost per disability adjusted life year averted) and budget impact.
d) Evaluate associations between mobility and TB transmission using whole-genome sequencing.
e) Project the potential reduction in population-level TB five-year incidence achievable through holiday-time rural screening and off-peak urban screening, using an individual-based transmission model.
f) To inform bioethical analysis by describing the experiences, attitudes, and preferences of patients with TB and their household contacts regarding household contact investigation.

Overall Anticipated Study TImeline:

Activity	2019		2020				2021				2022				2023				2024	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Protocol development																				
IRB & local/provincial approval																				
Database development																				
Hire & train study staff																				
Site preparation																				
Enrollment of participants																				
Data collection & cleaning																				
Empirical costing																				
Whole genome sequencing																				
Epidemiological data analysis																				
Bioethics data collection																				
Genomic data analysis																				
Dissemination of findings																				

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Tuberculosis (TB) remains a global health emergency, responsible for 10 million new cases in 2017.[1,2] It is the world's leading infectious disease killer, causing 1.3 million deaths annually,[1] despite the availability of cheap curative treatment for the vast majority of cases.[3] Worldwide, TB incidence has been declining since 2004 at a rate of only 2% per year.[1] The global community has recognized that this rate of progress – with declines in incidence nearly matched by population growth – is unacceptable for a curable disease, and the World Health Organization (WHO) has set very ambitious targets for ending the global TB epidemic.[4] To meet interim milestones, including a 50% reduction in TB incidence by 2025, novel approaches are urgently needed.[5]

Arguably, the greatest impediment to achieving marked reductions in TB incidence and transmission is delayed (or entirely missed) detection of individuals with active TB in high-burden settings. An estimated 3.6 million people with incident TB (>30% of all cases) were "missed" – i.e., never reported to public health authorities – in 2017.[1] Furthermore, national prevalence surveys suggest that the average duration of culture-detectable TB (as estimated by the incidence/prevalence ratio) is one year or more.[6] The inability of more sensitive diagnostic tests (such as Xpert MTB/RIF[7]) to substantially reduce TB morbidity[8-12] suggests that, even with available highly sensitive tests, patients with TB are being diagnosed very late in their disease course. This hypothesis is supported by evidence of declining TB mortality in most countries (suggesting better diagnosis and treatment), but without a corresponding decline in incidence or prevalence (suggesting that treatment is occurring too late to prevent transmission).[1,13]

TB transmission is demographically heterogeneous[14] – including three dimensions that are highly consistent across epidemiological settings. First, in high-burden settings (particularly those in sub-Saharan Africa), the majority of TB disease occurs in young adults (ages 15-49)[15]; even in low-burden countries like the United States, where the elderly face higher TB rates because of greater exposure to TB in the past,[16] the longitudinal risk of TB over the lifespan is greatest during the young adult.[17] Second, it is increasingly recognized that men account for a preponderance of TB in nearly every country6 – a gender gap that may partially reflect poorer access to healthcare (or lower willingness to access healthcare), but that also likely reflects differential social mixing patterns,[15] higher likelihood of living in congregate settings (particularly prisons[18]), and other poorly characterized (e.g., biological[7]) factors.[19] Third, TB is the quintessential disease of poverty; more impoverished individuals almost universally experience higher rates of TB.[20,21] As with the gender and age gaps, some of this disparity can be explained by known factors (e.g., malnutrition,[22] crowding[23]), but other unknown factors likely also play an important role. Regardless of the mechanistic causes of these three sources of demographic

heterogeneity, they result in an unfortunate reality, namely that the populations most likely to have and to transmit TB are also the populations (young adult, male, poor) that are hardest to reach through existing interventions that rely on the routine healthcare system.

A hallmark of these high-TB-risk demographic groups is their high level of mobility and migration. While the motivations for human movement are diverse, two major patterns include migration to urban centers for employment and return to homelands to spend time with families. Such mobility is common in many developing country settings,[24,25] and can result in temporary population spikes in "destination" areas of 125%.[26] South Africa is emblematic of these patterns, with a recent net population shift from rural to urban areas,[27] a population of temporary migrants overwhelmingly comprised of males age 20-45 years,[28] and the majority of its tourism representing trips for visiting family and relatives.[29] Internal migration has been linked with HIV (a major risk factor for TB): in KwaZulu Natal, South Africa, the prevalence ratio for HIV, comparing migrants to non-migrants in the same neighborhood, was 1.65 and increased with the number of moves.[30] Recent migrants are less likely to utilize health services in South Africa,[31] and are at higher risk of all-cause mortality as well as mortality due specifically to HIV/TB.[32] Recent studies have shown that migration likely plays an important role in the transmission of extensively drug resistant TB (XDR-TB)—among 1084 genomically linked case-pairs in KwaZulu Natal, the median distance between case-pairs was 108 km, and half of all case-pairs resided in Durban, the urban center of the province, while the other half resided in rural areas.[33] Finally, studies from China and Tajikistan show that migrants are less likely to be appropriately treated for TB, and at higher risk for loss from care, treatment failure and death than non-migrant counterparts.[34,35] Given the strong demographic correlation between mobility and TB disease risk, co-location of major TB risk factors (e.g., HIV) among migrants, and poorer TB treatment outcomes associated with migration, better understanding of the spatial and temporal dynamics of TB transmission – including the design of effective interventions – among highly mobile populations will be essential if we are to make substantive progress toward ending TB in high-burden settings. In South Africa, which bears the fifth-largest burden of incident TB in the world, household contact investigation is recommended as a key component of the national TB strategic plan for HIV, TB, and sexually transmitted infections.[36] Household contact investigation entails visits by healthcare workers to the homes of individuals diagnosed with TB, in order to identify household members who may have TB infection or disease.[37] As high-burden countries pursue increasingly ambitious goals for ending TB, the importance of household contact investigation is likely to increase worldwide.[38] Furthermore, household contact investigation provides an ideal opportunity to offer HIV counseling and testing.[39] However, the practice of household contact investigation also presents both logistical and ethical challenges. For example, one must weigh the deontological value of protecting confidentiality to prevent stigma and blame of the individual diagnosed with TB against the utilitarian perspective of protecting the household and broader community health against infection.[40]

Our unique research collaboration can provide novel insights into migration and TB transmission. To better understand the interplay between mobility and TB transmission, it is important to compare patterns of TB disease and transmission in representative rural and urban settings. Our research infrastructure is ideally placed to make this comparison. Specifically, for

this proposed research, we will combine three research sites: two in rural Limpopo province (located in northern South Africa along the border with Botswana, Mozambique and Zimbabwe) and one in the Soshanguve township of urban Tshwane and surrounding areas. Relative to other provinces in South Africa, Limpopo is more representative of sub-Saharan Africa as a whole, with a low (<50/km2) population density, a lower – though still extremely high – TB prevalence (300 per 100,000), and the lowest per capita gross domestic product ($3,500 USD).[41] Johns Hopkins University (JHU) and the Perinatal HIV Research Unit (PHRU) of the University of the Witwatersrand have been conducting studies of active TB case finding in Limpopo Province since 2014.[42] Many residents of Limpopo migrate south toward Tshwane and Johannesburg for work. Tshwane Municipality is the northernmost urban area in Gauteng Province, and has a TB incidence rate of 330/100,000). One Tshwane township in particular, Soshanguve, (the name of which is itself a concatenation of ethnic groups from Limpopo) is densely population (1,100 residents/km^2) has a large number of immigrants and migrants from Limpopo. Setshaba Research Centre has been located and working in Soshanguve since 2004 and has conducted over 30 clinical and social science studies in the area, with a focus on HIV and TB.[43-61] Setshaba has developed long-term partnerships with local government representatives and community leaders in the area which will facilitate recruitment and enrollment of the proposed study population. Our research collaboration is therefore uniquely placed to answer questions about TB transmission and mobility by combining high-quality infrastructure in a rural homeland province with that an urban settlement to which many residents migrate.

2.2 Rationale

It is not sufficient merely to understand TB transmission patterns; we must also design and evaluate interventions to find the “missing” cases of TB in these high-risk mobile populations. Although the household setting does not account for all (or even the majority of) TB transmission in South Africa,[62] households remain the highest-yield location for TB systematic screening.[63] Characteristics of effective case-finding interventions will include: (a) ability to identify cases who are not found (or found only very late) by the routine healthcare system; (b) feasibility of implementation;[64] (c) cost-effectiveness[65] and (d) potential to reduce TB incidence at the population level.[66] Taking these considerations into account, we propose to evaluate the effectiveness, implementation, cost-effectiveness and potential impact of two innovative approaches to TB case detection in a highly mobile South African population: holiday-based contact investigation in rural homelands and “off-peak” (evening/weekend) household screening in an urban township. We will investigate associations between mobility patterns and TB transmission using a multidisciplinary approach that includes detailed epidemiological investigation, genomic epidemiology, and transmission modeling; this will be combined with a rigorous evaluation of the interventions themselves, including both their effectiveness in identifying additional cases and each intervention’s implementation in terms of reach, feasibility, fidelity, cost-effectiveness, and maintenance. This research has the potential to transform our approach to finding the “missing 3.6 million” TB cases by recognizing a major sociodemographic

driver of missed and delayed diagnosis – human mobility – and implementing solutions that are tailored to the needs of the highly mobile populations that bear a disproportionate burden of TB morbidity and likely also generate a disproportionate share of TB.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Our surveys are designed to pose only minimal risk to participants. The primary risk to patients in this study is a breach of confidentiality. Participants will be asked to provide potentially sensitive information (e.g., participant home address, socioeconomic status, patient TB status), and while every effort will be made to maintain those data in confidential and secure fashion, it is possible that such data could become known by individuals other than study personnel. Participants will be informed of this risk and given the opportunity to decline participation without any negative impact on their clinical care. Patients will also be offered HIV testing, which carries a risk of emotional distress with a positive result. All study staff who perform HIV testing will first be trained in appropriate HIV Testing and Counseling (HTC); no HIV tests will be performed, nor results provided, without appropriate corresponding counseling. Patients (for example, those testing newly HIV positive) who require additional clinical care will be promptly referred to routine clinical services for management. Patients may also experience inconvenience due to the time required to complete the survey, including a sense of intrusion from household visits. We will thoroughly train data collection staff to maintain discretion during participant interactions and to respect the privacy of each participant. Data collection activities will be ceased immediately if requested by the participant at any point during the study. For participants who take part in focus group discussions, although we will stress confidentiality, we cannot assure it due to the group nature of this interaction.

2.3.2 Known Potential Benefits

The proposed research may provide a direct benefit to household contacts who are enrolled in this study, as it may facilitate more rapid diagnosis of TB or HIV, which would in turn facilitate more rapid treatment, thus improving survival and reducing additional transmission to loved ones. Index cases are unlikely to derive direct benefit from participating in the study, but their families may benefit as above. We also aim to conduct this research in such a way as to provide maximum benefit to the community; we will actively disseminate our results to decision-makers within our study districts in Limpopo and North West and Gauteng provinces, and anticipate that our findings may influence policy, enabling the implementation of interventions that can reduce TB incidence in the affected communities. Our research is specifically designed to evaluate the potential benefits to these communities, in terms of acceptability, effectiveness in finding new cases of TB (and starting them on treatment), and impact on incidence at the population level.

3 OBJECTIVES

Primary:
To measure the comparative effectiveness of two novel household-based TB contact investigation strategies: 1) tracing on holidays in rural areas; 2) tracing on evenings and weekends in urban areas: each of these compared to tracing during working hours (standard household contact tracing).

Secondary:
1. To compare the implementation, effectiveness, cost-effectiveness and potential impact of rural holiday and urban off-peak contact investigation against standard contact investigation in South Africa

a) Assess the effectiveness of each novel strategy compared to standard contact tracing by setting (rural versus urban).
b) Examine metrics of acceptability, feasibility, fidelity and sustainability for each novel strategy relative to standard contact investigation.
c) Measure costs of each intervention and estimate cost-effectiveness (incremental cost per disability adjusted life year averted) and budget impact.
d) Evaluate associations between mobility and TB transmission using whole-genome sequencing.
e) Project the potential reduction in population-level TB five-year incidence achievable through holiday-time rural screening and off-peak urban screening, using an individual-based transmission model.

2. To inform bioethical analysis by describing the experiences, attitudes, and preferences of patients with TB and their household contacts regarding household contact investigation

a) Assess participants' experiences of inconvenience and stigma (personal and family/community), attitudes toward confidentiality and importance of contact investigation, motivation to participate in household contact investigation, and preferences for disclosure.

b) To evaluate the degree to which offering routine HIV testing influences beliefs about TB/HIV co-morbidity and affects thinking about stigma, blame, and duty to others' health during household contact investigation.

4 STUDY DESIGN

In this study, we will evaluate two innovative approaches to household contact investigation, namely holiday-time contact investigation in a largely rural province (Limpopo) and evening-time contact investigation in a peri-urban township (Soshanguve in Gauteng province and surrounding areas within North West province). These approaches leverage known patterns of movement and migration in sub-Saharan Africa and throughout the world, namely that younger working individuals (i.e., those at greatest risk of TB and TB transmission) often immigrate from rural to urban areas, spending evenings after work in their urban homes, and returning to their rural family homesteads for major holidays. We will compare each of these approaches to each other and to standard household contact investigation during business hours from 8 am to 4 pm Monday through Friday in each setting, with a primary outcome of the number of additional cases of TB identified per index case and secondary outcomes of implementation, cost-effectiveness and transmission, thus identifying feasible strategies that can be more efficient (per dollar invested) in finding additional cases of TB.

We propose to conduct a four-arm parallel randomized trial, using the following strategies (See study schematic below):

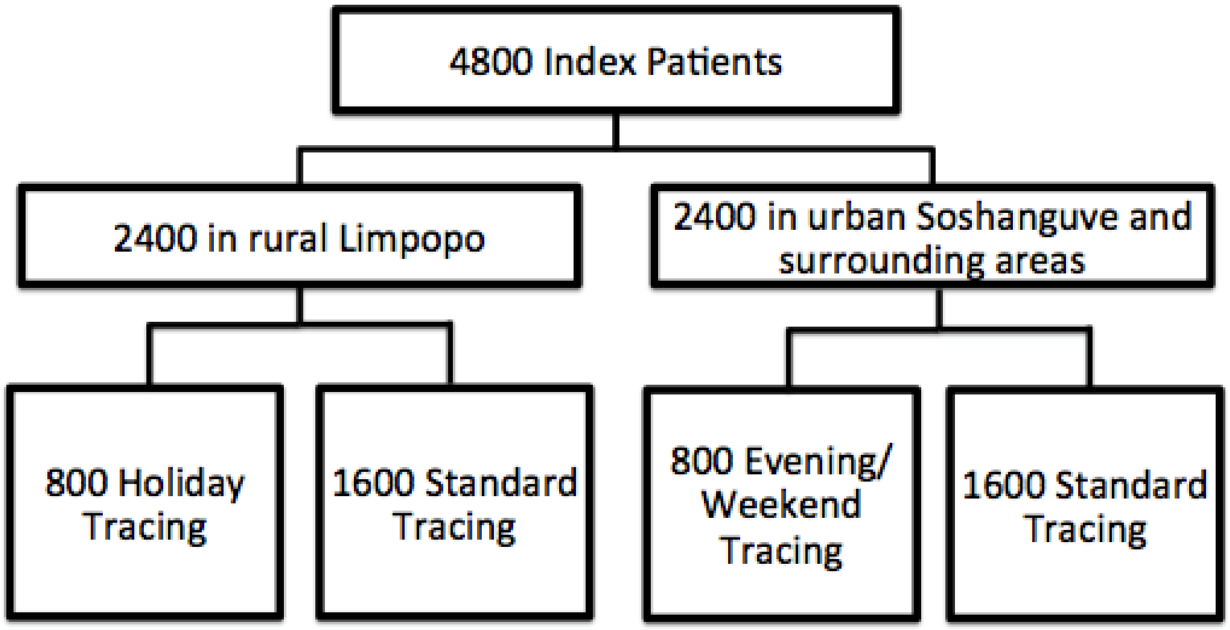
1. **Routine contact investigation in rural Limpopo**. Study staff will perform routine contact investigation of TB cases diagnosed in study hospitals in Limpopo, throughout the year. Contact investigation will be performed on weekdays during business hours.
2. **Holiday contact investigation in rural Limpopo**. At the time of diagnosis, study staff will ask TB cases diagnosed in Limpopo study hospitals for consent to perform deferred household contact investigation over a three week period during the Easter holiday (for cases diagnosed between January 1 and Easter) or a five week period during the Christmas holiday (for cases diagnosed between Easter and December 31). These holiday periods will align with the public school holidays in South Africa as detailed by the National Education Policy Act School Calendar.
3. **Routine contact investigation in urban Soshanguve and surrounding areas**. Study staff will perform routine contact investigation of TB cases diagnosed in study clinics in Soshanguve, throughout the year. Contact investigation will be performed on weekdays during business hours.
4. **Off-peak contact investigation in urban Soshanguve and surrounding areas**. Study staff will perform contact investigation of TB cases diagnosed in study clinics in Soshanguve, throughout the year. Contact investigation will be performed during evenings and weekends.

Bioethics sub-study

We will perform a mixed-methods investigation of the ethics of household contact investigation for TB among participants from the parent study (both TB index cases and their household contacts) after they complete TB evaluation. This investigation will include a combination of focus group discussions (six groups of 10 participants each), in-depth interviews (24 interviews), and quantitative surveys (300 participants). Each of these investigations will follow a 2x3 factorial design, including equal representation of household contacts and index patients across

each of the three study districts.

Study Schematic



5 STUDY POPULATION

5.1 Selection of the Study Population

Sample Size

We anticipate enrolling a total of 14,400 participants. We make no exclusions based on sex, age or race for enrolment, therefore we expect that our final enrolled study population will be roughly representative of those living within the study area.

These 14,400 will include:
- 1600 index cases in the routine contact investigation arm in Limpopo
- 1600 index cases in the routine contact investigation arm in Soshanguve and surrounding areas
- 800 index cases in the holiday contact investigation arm in Limpopo
- 800 index cases in the off-peak contact investigation arm in Soshanguve and surrounding areas
- 9,600 contacts (a mean of two contacts per case, accounting for some cases who will not have any contacts, based on our enrollment of household contacts in our recent trial in Limpopo)

Study Population Sources

Index cases will represent a sample of consecutive consenting individuals diagnosed with pulmonary TB (including microbiological and/or chest x-ray diagnosis) from twelve hospitals in Vhembe and Capricorn Districts of Limpopo, and 33 primary health care clinics and two district hospitals in Soshanguve and surrounding areas. The only exclusion criteria will be a plan not to pursue treatment within the study district (as this would make contact investigation infeasible in the programmatic setting), and being on TB treatment for longer than one month (as these cases will likely be negative by liquid culture in order to identify transmission links between cases using whole genome sequencing). Note that contacts do not have the same requirement of planning to pursue treatment within the district; thus, it is possible – and expected – that holiday contact investigation in Limpopo will yield cases from outside the district, for example. Individuals who later decline to have contact investigation performed (or who, for example, provide false contact information thus making contact investigation infeasible) will still be included in the study sample and in the denominator for all analyses. Our aim is to make the population of this study as representative as possible as the target population for the proposed intervention. Eligible participants in the bioethics sub-study will include all individuals who were enrolled in the parent study and completed follow-up for the primary outcome (including those who declined or were ineligible to participate in household contact investigation). We will enroll consecutive eligible participants in each district until our desired sample size (64 evaluable index cases and 64 evaluable household contacts from each district) has been attained.

Eligibility Criteria

Subjects in each of the below participant categories must meet each eligibility criteria for that category:

TB index cases:
Inclusion criteria:

- Age 0-99 years (Including those recently deceased)
- Diagnosed with pulmonary TB at a study hospital or clinic (microbiological and/or chest x-ray diagnosis)

Exclusion criteria:

- Unwilling/unable to provide informed consent (including next of kin, for those recently deceased)
- Plan not to pursue TB treatment within the study district
- Unwilling/unable to comply with study procedures

Contacts:
Inclusion criteria:

- Age 0-99 years (18-99 for the bioethics sub-study)
- Currently resides with or visiting eligible TB index case

Exclusion Criteria:

- Unwilling/unable to provide informed consent
- Unwilling/unable to comply with study procedures

6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

Recruitment
Within Limpopo Province, we will have two study sites, one in Vhembe and one in Capricorn district and these sites will recruit participants from a total 12 hospitals. In Tshwane (across both North West and Gauteng provinces) we will have one site in Soshanguve, and this will recruit participants from 33 clinics and two district hospitals. Within each site and clinic/hospital, we will seek to enroll all consecutive patients meeting the following inclusion criteria: (a) diagnosed with pulmonary TB at one of the study health facilities (including microbiological and/or chest x-ray diagnosis); (b) plan to pursue treatment within the study district; (c) willingness to provide informed consent and comply with study procedures. We will also include those patients who are recently deceased from the hospital register. Eligible participants will be identified by weekly review of the presumptive TB and TB treatment registers in each location, also in close collaboration with healthcare staff in each study health facility. We will approach all potentially eligible participants for informed consent at their treatment location within two weeks of diagnosis, making phone calls as necessary to contact participants who have been lost to follow-up between diagnosis and treatment initiation. For patients who are recently deceased, the next of kin will be contacted and asked if they can consent for the patient's information to be included in the study. Next of kin will also be asked to provide temporary consent for index patients who are too ill to consent at the time of enrollment. (These patients will be re-approached for consent once they have recovered to the extent of being able to complete the consent process.) After providing informed consent, participants will be randomized via a computer-generated algorithm to either routine or novel (holiday or off-peak) household contact investigation. Of note, participants who after consent and randomization, decline to accept household contact investigation – or who cannot be located at home at the time of home visit, will be included in the primary analysis as not resulting in a secondary case detected. Recruitment will be continued until 2400 participants are enrolled in each arm (expected to be completed within 28 months). For the bioethics sub-study, eligible participants will include all individuals who were enrolled in the parent study and completed follow-up for the primary outcome (including those who declined or were ineligible to participate in household contact investigation). For this sub-study, we will enroll consecutive eligible participants in each district until our desired sample size (˜64 index cases and ˜64 evaluable household contacts from each district) has been attained.

Data Collection: Contact tracing and interviews
Upon enrollment, we will conduct a detailed interview of all index cases, based on our current case report forms used in Limpopo. These interviews will include demographic, socio-economic and clinical characteristics, detailed data on mobility and migration, the preceding diagnostic cascade and symptom history, and extensive assessment of costs (including catastrophic health expenditures). Experience suggests that we can collect these data in 30 minutes. For patients

who are deceased or too ill to participate, the next of kin will complete the interview to the best of their ability. We will also collect a sputum sample from each living index case which will be sent for liquid MGIT culture in order to perform whole genome sequencing. After completing the interview, for cases assigned routine or off-peak contact investigation, an appointment time in the next two weeks will be arranged for the household visit. Cases allocated to holiday-time investigation will be asked for contact information and will be called within two weeks of the holiday to remind them of the study and set an appointment time for the household visit.

Study teams (2 in Limpopo and 2 in Soshanguve) consisting of a nurse and a research assistant trained in HIV counselling and testing will visit the household of each consenting index case (or legal guardian, in the case of minors). At the household, teams will recruit all available household members of all ages. For each enrolled participant, the team will conduct a similar interview to the index case on demographic, socio-economic, mobility/migration, health seeking behavior and clinical characteristics. Specifically, mobility questions will focus on spatial and temporal movement patterns over the previous year and will include: number and duration of trips away from primary residence, total duration of time away, destination and purpose of trips, longest distance travelled, longest trip duration, length of time living at primary residence and total number of lifetime moves. Each participant will be screened for TB as described above. Results on Xpert testing will be monitored by study staff using the electronic NICD laboratory system (tier.net), and participants will be notified either by phone or in person at a household visit if they have tested positive for TB and referred to the nearest public-sector clinic for treatment.

Empirical Assessment of Costs

We will conduct an empirical costing and associated cost-effectiveness analysis of the four contact investigation strategies from the societal perspective. Costs will be measured prospectively from study data and will comprehensively include those related to both health systems and patients. Health systems costs will be captured using an “ingredients” through a combination of budgetary review, key informant interviews (e.g., administrative staff), direct observation (e.g., time-motion studies of patients and study staff), and prospective logbooks kept by study staff and other relevant personnel (e.g., clinic nurses) Patient-level costs will be measured through patient interview, using the WHO Handbook on Tuberculosis Cost Surveys as a guide. We will also include other costs incurred by society, including additional costs to the national disability grant system (for which most TB patients are eligible), costs to the community “safety net” associated with having to perform contact investigation outside of regular business hours (e.g., any security concerns, childcare and other expenses for healthcare staff), and costs to caregivers to help patients complete the process of initiating TB treatment (for contacts who test positive). Costs from this “ingredients” approach will be compared (as a check) to a “top-down” approach in which we estimate large cost items (e.g., annual staff salaries) and divide those costs by the number of new TB cases identified and starting treatment under each strategy. We will also perform additional calculations for budget impact analysis, including estimating the size of the eligible population, the current number receiving contact investigation and the expected number receiving contact investigation after introducing novel implementation strategies, and any changes expected in TB-related costs following the introduction of this intervention.

Bioethics sub-study

Quantitative surveys
After obtaining written informed consent, trained data collectors will meet with participants either at their homes or in study clinics according to participant preference. Surveys will be conducted in the participant's choice of English or the local language in each district, and answers will be entered directly into an electronic database by study staff using mobile tablets. The interview will be pilot tested by study staff and designed to last a maximum of 30 minutes. Surveys will include participants' level of agreement with importance of household contact investigation; willingness to participate in household contact investigation; preferences for TB/HIV status disclosure; if (and to what extent) HIV testing contributes to the misconception that all people with TB have HIV; and whether HIV testing affects willingness to participate in household contact investigation. Question formats will include Likert scales, discrete choice experiments, best-worse scales, contingent valuation, and validated multi-item instruments (e.g., van Rie stigma scale[25]). All data will be securely transmitted into a password protected REDCap database. The study data manager will routinely check all uploaded records daily for completeness, will run in- depth queries on a weekly basis, and ensure that all queries are resolved.

Qualitative interviews/focus group discussions
Each semi-structured, in-depth interview will be approximately one hour in length and will cover the following domains: TB/HIV disclosure preference, perceived stigma/blame, importance of household contact investigation, willingness to participate in household contact investigation, family invasiveness, community stigma/blame, duty to others health, and beliefs about TB/HIV confection. Six focus groups of ten participants each will be conducted in a private room at a central hospital in each district. Focus group discussions will last approximately two hours and will feature discussions on community-level perceptions and norms regarding the ethics of household contact investigation. No personal identifiers will be collected or used during the discussion. All in depth interviews and focus group discussions will be audio recorded, transcribed, translated as needed, and coded using Atlas.ti or NVivo. Thematic content analysis will be conducted to explore and document themes relating to participants' experiences, attitudes, and preferences in each domain.

6.2 Laboratory Evaluations

6.2.1 Laboratory Evaluations/Assays

Liquid MGIT culture

Liquid MGIT culture is a mycobacterial growth assay that detects the presence of *Mycobacterium tuberculosis* directly from sputum. Xpert MTB/RIF assays will be carried out on sputum samples collected from participants. This assay will not be conducted under research conditions, but as part of routine South African standard of care, by the National Institute For Communicable Diseases (NICD). Sputum samples collected from

participants will be couriered by team couriers to NICD central laboratory for MGIT testing (see 6.2.3.2).

6.2.2 Special Assays or Procedures

Whole Genome Sequencing (WGS)

During the period of enrollment, we will work with the National Health Laboratory Services to perform culture and whole genome sequencing on all positive sputa. Bacterial isolates from standard culture will have total DNA extracted by staff at the NICD laboratory. WGS will be performed on the Illumina NextSeq platform. Nextera XT kit will be used to prepare libraries. Paired-end sequencing will be done with read-lengths of 250 bp at >50x coverage. Alignment to a reference strain (H37Rv), variant filtering, and variant comparison will flow through a pipeline of five open-source tools (FastQC, BWA, Samtools, Freebayes, and Bedtools) following criteria commonly used in genomic analyses.

6.2.3 Specimen Collection, Preparation, Handling and Shipping

6.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

Sputum collection is a routine clinical procedure that does not place the participant at any risk, and will be conducted by study staff only at household visits—the remainder of sputum collection for the study will be conducted by local clinic staff according to the standard of care. The participant will be instructed to go outside to provide the sputum sample. They should take several deep breaths, and hold each for 5 seconds, then cough such that sputum, if any, comes into their mouth. The participant then spits the sputum into the sputum collection jar and seals the lid on top, before handing to the study staff who then labels the specimen with participant details according to South African Department of Health standard procedures and places it inside of a sealed plastic bag then into a cooler until it is handed off to the NICD courier for transport to the NICD laboratory. At the laboratory, the sputum is processed immediately and tested by the Xpert MTB/RIF assay. No specimen is retained by the laboratory after testing

6.2.3.2 Specimen Shipment

Sputum specimens in closed vials inside of a sealed bag are transported by NICD courier to the central NICD laboratory according to standard NICD procedures. This occurs 1-2 times on each weekday, and the timing is variable by clinic. Specimens are kept at 4°C in a cooler until reaching the laboratory. Specimens for WGS will be transported by NICD courier to the NICD headquarters in Johannesburg as above, on a bi-weekly basis by courier.

7 STUDY SCHEDULE

7.1 Screening and Enrollment

Within Limpopo Province, we will have two study sites, one in Vhembe and one in Capricorn district, while in Tshwane municipality we will have one site covering Soshanguve and surrounding areas. Within each site, we will seek to enroll all consecutive patients meeting the eligibility criteria. Potential eligibility will be assessed weekly review of the presumptive TB and TB treatment registers at each study facility, in close collaboration with healthcare staff in each hospital. We will approach all potentially eligible participants for informed consent at their treatment location within two weeks of diagnosis, making phone calls and/or home visits as necessary to contact participants who have been lost to follow-up between diagnosis and treatment initiation.

All individuals present at the household at the time of a household study visit will be considered eligible for enrollment as contacts, and all adults approached during the timing of the bioethics sub-study will be considered eligible for enrollment into that sub-study.

7.2 Enrollment/Baseline, if applicable

See above.

7.3 Follow-up and Final Visits, if applicable

Not applicable, unless the participant is a household contact who is diagnosed with TB or selected for the bioethics sub-study. For household contacts, we will perform a follow-up visit to relay results and refer for treatment, however no other study-specific procedures will be performed at this visit. For the bioethics sub-study, all procedures will be completed during a single follow-up visit (during which no personal identifiers will be recorded).

7.4 Early Termination Visit, if applicable

Not applicable.

7.5 Criteria for Discontinuation or Withdrawal of a Subject (or a Cohort), if applicable

Participants may withdraw from the study voluntarily at any time, but there are no further criteria for discontinuation or withdrawal.

8 ASSESSMENT OF OUTCOME MEASURES

8.1 Specification of the Appropriate Outcome Measures

8.1.1 Primary Outcome Measure

The effectiveness of contact tracing, measured as the number of secondary cases identified and started on treatment per index case, comparing households in the novel arm to households in the standard arm.

8.1.2 Secondary Outcome Measures

1. **The TB prevalence ratio, comparing highly mobile to less mobile individuals**, measuring mobility on two scales (neighborhood/intra-urban and regional/intra-national).
2. **Relative acceptability of each novel strategy**, compared against routine contact investigation. We will create a continuous score from the acceptability interview questions (provided to a randomly selected 15% of the population), with a higher score indicating greater acceptability of the contact tracing strategy.
3. **Feasibility of each strategy** as the proportion of potentially eligible index cases for whom a household visit was conducted.
4. **Relative fidelity of each novel strategy** using a process checklist for each index case and household, including whether the household visit was offered and accepted, whether the visit was attempted, whether the visit was successful (i.e., enrolled at least one contact), whether symptom screening and sputum collection were completed and whether newly identified TB cases were notified and referred for treatment.
5. **Sustainability of each novel strategy** by reporting the primary outcome and fidelity measures according to six-month time period over the course of the study.
6. I**ncremental cost-effectiveness ratio for each novel strategy.** defined as (cost of contact tracing strategy 2 – cost of strategy 1)/(effectiveness of strategy 2 – effectiveness of strategy 1), where effectiveness is modeled as the number of disability-adjusted life years (DALYs) averted by the intervention. The primary cost-effectiveness measures will be the incremental cost per DALY averted using novel strategies (holiday and off-hours contact tracing) compared to routine contact tracing in each setting separately.

7. **Experiences of inconvenience, attitudes toward confidentiality, motivation to participate, and preferences for disclosure**, assessed through both thematic analysis of in-depth interviews and focus group discussions and quantitative analysis of discrete choice experiments and best-worst scaling.

9 SAFETY ASSESSMENT AND REPORTING

9.1 Definition of Adverse Event (AE)

As our intervention is the implementation and observation of routine South African standard of care (contact tracing of newly identified TB cases), we do not anticipate any medical adverse events which may occur as a result of this research study. Therefore, AEs (including SAEs) will not be recorded and reported for this study.

9.2 Definition of Serious Adverse Event (SAE)

N/A—see 9.1 “Definition of Adverse Event”

9.3 Reporting Procedures

N/A—see 9.1 “Definition of Adverse Event”

9.3.1 Serious Adverse Event Detection and Reporting

N/A—see 9.1 “Definition of Adverse Event”

9.3.2 Reporting of Pregnancy

This is a cross-sectional study which makes no attempt to exclude pregnant women. Pregnancy does not represent a complication within the context of this research study. Pregnancy status of any enrolled participant will be documented.

9.3.3 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

TB cases detected through this study are referred for care to their closest public health clinic for further evaluation and treatment, according to the South African standard of care. As TB is a measured outcome of this study, and detection of TB is the overall goal, it is not considered an AE or SAE.

9.3.4 Type and Duration of the Follow-up of Subjects After Adverse Events

N/A—see 9.1 “Definition of Adverse Event”

10 CLINICAL MONITORING STRUCTURE

Site monitoring is conducted to ensure that the human subject protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that the study is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the funder of the project, or its designee may conduct site-monitoring visits.

Site visits may be made at standard intervals and may include, but are not limited to, review of regulatory files, informed consent forms, laboratory reports, and protocol and GCP compliance. Site monitors will have access to the study site, study personnel, and all study documentation. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11 STATISTICAL CONSIDERATIONS

11.1 Study Outcome Measures

Primary Outcome Measure:

Our primary effectiveness outcome will be the ratio of the number of secondary TB cases identified and started on treatment per index case, comparing index cases allocated to the novel strategy (off-peak screening in Soshanguve and holiday screening in Limpopo) to those receiving standard contact investigation.

Secondary Outcome Measures:

1. **The TB prevalence ratio, comparing highly mobile to less mobile individuals**, measuring mobility on two scales (neighborhood/intra-urban and regional/intra-national). For the former, we will estimate the number of kilometers traveled on a daily basis (secondary analysis: amount of time spent in transit), truncating long excursions at 50km (one hour).
2. **TB strain relatedness using maximum likelihood transmission trees.** We will integrate TB natural history, epidemiological, and WGS-derived phylogenetic data into a statistical modeling framework to draw probabilistic conclusions about the likelihood of transmission between persons. “Transmitters” will be defined as individuals from whom at least one secondary case most likely originated.
3. **Relative acceptability of each novel strategy**, compared against routine contact investigation. We will measure acceptability of the intervention among index cases and contacts using a short questionnaire given to a randomly selected participant at a randomly selected 15% of the households visited. The interview will cover acceptability of the visit timing, notification, visit activities (TB screening, HIV testing) and study team interaction among others.
4. **Feasibility of each strategy** as the proportion of potentially eligible index cases for whom a household visit was conducted. We will also record all reasons why visits were unable to be conducted (e.g. could not find household, no one ever home, visit not conducted during expected off-peak period).
5. **Relative fidelity of each novel strategy** using a process checklist for each index case and household, including whether the household visit was offered and accepted, whether the visit was attempted, whether the visit was successful (i.e.,

enrolled at least one contact), whether symptom screening and sputum collection were completed and whether newly identified TB cases were notified and referred for treatment.

6. **Sustainability of each novel strategy** by reporting the primary outcome and fidelity measures according to six-month time period over the course of the study.
7. **Incremental cost-effectiveness ratio for each novel strategy.** defined as (cost of contact tracing strategy 2 – cost of strategy 1)/(effectiveness of strategy 2 – effectiveness of strategy 1), where effectiveness is modeled as the number of disability-adjusted life years (DALYs) averted by the intervention. The primary cost-effectiveness measures will be the incremental cost per DALY averted using novel strategies (holiday and off-hours contact tracing) compared to routine contact tracing in each setting separately.
8. **Experiences of inconvenience, attitudes toward confidentiality, motivation to participate, and preferences for disclosure**, assessed through both thematic analysis of in-depth interviews and focus group discussions and quantitative analysis of discrete choice experiments and best-worst scaling.

11.2 Sample Size Considerations

We estimate our sample size based on the assumption that 3% of household contacts will have tuberculosis (half the 6% prevalence seen in a previous study led by Dr. Martinson),[64] and that an average of two contacts per case will be screened in the routine arm (based on our ongoing trial in Limpopo). Thus, in the routine arm, we anticipate a mean of 0.06 secondary cases per index case. Given the additional complexity of holiday-time or off-peak screening, we power our analysis under the *a priori* belief that such interventions will not be reasonably implemented unless they result in a yield that is twice that under routine contact investigation. Assuming an average of two to five contacts per household and a high (0.68) between-household coefficient of variation of the outcome as found in [64], a comparison of n=1600 households (index cases) in the routine arm and 800 households (index cases) in the novel arm would have more than 99% power to detect this difference. If only half of the expected index cases are enrolled, the minimum power (two contacts per household) would be 84%. A maximally conservative estimate of sample size – assuming complete clustering of these cases at the household level, two contacts per household, and only 50% as many household cases as found previously – is described by a Poisson distribution of 0.06 secondary cases per index case.

We have selected our sample size to give more than 90% power to detect this most conservative difference. The table below provides estimates of our power to detect a statistically significant difference in the primary outcome.

Table. Power calculations. The power to detect each difference is given in italics; the primary comparison is between finding 0.06 secondary cases per index case in the routine arm and 0.12 in the novel screening arm.

		Mean number of secondary cases per index case, novel approach				
Mean number of secondary cases per index case, routine approach		**0.08**	**0.1**	**0.12**	**0.18**	**0.24**
	0.02	*>0.99*	*>0.99*	*>0.99*	*>0.99*	*>0.99*
	0.04	*0.99*	*>0.99*	*>0.99*	*>0.99*	*>0.99*
	0.06	*0.54*	*0.97*	*>0.99 (primary)*	*>0.99*	*>0.99*
	0.08	-	*0.44*	*0.93*	*>0.99*	*>0.99*

Randomization

Randomization will be performed using computer-generated random permuted blocks of varying sizes, with an allocation ratio of 2 (routine):1 (novel: holiday or off-peak). Randomization will be conducted separately for Limpopo and Soshanguve and surrounding areas (i.e., two separate randomization sequences will be generated for each site); and within Limpopo, randomization will be further stratified by district, thus ensuring 2:1 allocation within each district as well. The randomization schedules will be uploaded into the REDCap system, which will automatically output an allocation every time a new consented patient is added and the interview is completed. In Limpopo, randomization will be performed throughout the year; those patients who are allocated to holiday timing will undergo household contact investigation during Easter if they are enrolled between February 1 and the end of the two-week Easter holiday, whereas those patients enrolled between the end of the Easter holiday and December 31 will undergo contact investigation during Christmas.

11.3 Participant Enrollment and Follow-Up

We anticipate enrolling a total of 14,400 participants:

- 1600 index cases in the routine contact investigation arm in Limpopo
- 1600 index cases in the routine contact investigation arm in Soshanguve
- 800 index cases in the holiday contact investigation arm in Limpopo
- 800 index cases in the off-peak contact investigation arm in Soshanguve
- 9,600 contacts (a mean of two contacts per case, accounting for some cases who will not have any contacts, based on our enrollment of contacts in our current trial in Limpopo)

Among adults from the above groups, 384 individuals (192 index cases and 192 contacts) will be selected to participate in the bioethics supplement.

We plan a single visit to each participant, so follow-up is not considered in this study.

11.4 Analysis Plan

Primary Outcome:

Our primary effectiveness outcome will be the ratio of the number of secondary TB cases identified and started on treatment per index case in the novel strategy arm (off-peak screening in Soshanguve and holiday screening in Limpopo) compared to index cases receiving standard contact investigation. We will conduct separate analyses for each site (rural Limpopo and peri-urban Soshanguve). For the primary analysis we will conduct an unpaired t-test for the hypothesis that the difference between the number of secondary TB cases per index case is the same in the two study arms. A secondary analysis will be performed to adjust for index case demographics, socio-economic factors, self-reported health seeking behavior, and clinical characteristics such as HIV status and history of TB. As the majority of the index cases are expected to have no secondary cases, this will be conducted using a zero-inflated Poisson regression with robust standard errors to account for household and enrollment site clustering.

Secondary outcome measures:

1. **The TB prevalence ratio, comparing highly mobile to less mobile index patients**, measuring mobility on two scales (neighborhood/intra-urban and regional/intra-national). For the former, we will estimate the number of kilometers traveled on a daily basis (secondary analysis: amount of time spent in transit), truncating long excursions at 50km (one hour). Based on exploratory data analysis and consideration of generalizable numbers (e.g., multiples of 5 and 10), we will consider a binary measurement of “highly mobile” versus “less highly mobile” at a natural break near the midpoint of the data. We will then use log-binomial regression to adjust for *a priori* potential confounders that will include age, sex, socioeconomic status, and HIV status, and robust variance estimation to account for clustering by households. Analyses will be stratified by site. We will perform a similar analysis for regional/intra-national mobility, taking as the primary exposure variable the self-reported number of trips per year greater than 50km (secondary analysis: number of nights spent away from primary residence). For each measure of mobility, we will explore additional methods of modeling the exposure variable, including continuous (linear), using restricted cubic splines (which may yield less interpretable estimates of effect but more flexible incorporation of complex patterns in the data), and as a categorical (“dummy variable”) exposure – again at natural breaks in the data.

2. **TB strain relatedness using maximum likelihood transmission trees.** Along with standard genetic thresholds (i.e. SNP differences of <5) for assessing whether strains are related by transmission, we will construct a maximum-likelihood phylogenetic tree using RAxML and other tree estimation packages. We will then employ a Bayesian approach to infer transmission.[65,66] After separating the data into distinct putative transmission clusters using a probabilistic approach combining SNPs, timing, and location information, we will generate timed phylogenetic trees for each cluster using Bayesian Evolutionary Analysis Sampling Trees (BEAST).[116] We will then use a stochastic, continuous-time Monte Carlo Markov Chain (MCMC) representing a branching transmission model. We will model within-host evolution of *Mtb* assuming a neutral coalescent process and generate transmission trees using an MCMC approach.[65,67] We will weight candidate transmission trees based on likely or unlikely linkages (e.g., household contacts). This method integrates TB natural history, epidemiological, and WGS-derived phylogenetic data into a statistical modeling framework to draw probabilistic conclusions about the likelihood of transmission between persons. “Transmitters” will be defined as individuals from whom at least one secondary case most likely originated.
3. **Relative acceptability of each novel strategy**. We will create an acceptability score from the interview questions, with a higher score indicating greater acceptability of the contact tracing strategy. We will use multivariable generalized linear regression model with a suitable link to model the acceptability score, with the primary exposure of interest being each novel contact investigation strategy (i.e off-hours tracing in Soshanguve, holiday tracing in Limpopo), relative to standard contact investigation in each setting. Analyses will be stratified by site
4. **Feasibility of each strategy** as the proportion of potentially eligible index cases for whom a household visit was conducted. We will also record all reasons why visits were unable to be conducted (e.g. could not find household, no one ever home, visit not conducted during expected off-peak period). Analyses will be stratified by site
5. **Relative fidelity of each novel strategy** using a process checklist for each index case and household, including whether the household visit was offered and accepted, whether the visit was attempted, whether the visit was successful (i.e., enrolled at least one contact), whether symptom screening and sputum collection were completed and whether newly identified TB cases were notified and referred for treatment. We will model fidelity as a binary outcome, using log-binomial regression, with the primary exposure of interest being novel versus standard contact investigation (separately in each setting), adjusting for potential confounders (for example, socio-demographic and clinical factors) and enrollment site as with the acceptability outcome and robust standard errors for multiple outcomes per household. Analyses will be stratified by site

6. **Sustainability of each novel strategy** will be accomplished by incorporating an indicator variable for the six-month time windows of the study period into the multivariable regression models of acceptability and fidelity outcomes described above, and evaluating for interactions between this time window indicator and the primary exposure variable (i.e. investigation arm).

7. **Cost-effectiveness ratio for each novel strategy.** Outcome measures will be derived by combining study data on patient characteristics (e.g., demographics, HIV status) and intervention effectiveness with literature estimates on key parameter values (e.g., disability weights,[68] sensitivity of Xpert Ultra,[69] and notified data on treatment outcomes[1]) to construct a Markov model of a population of individuals who are eligible for TB screening under each strategy. In performing this evaluation, we will follow standard guidance for economic evaluation, including inflation using South Africa's GDP deflator, conversion to a common currency (US dollars) and year, discounting of all future costs and effectiveness, and measurement of costs as economic (opportunity) costs.[70,71] We will conduct one-way sensitivity analyses of all model parameters and multi-way sensitivity analyses of those parameters found to be most influential, in order to provide insight into the major drivers of cost-effectiveness and the settings in which each contact tracing strategy is likely to be preferred. We will also perform a probabilistic sensitivity analysis (using beta distributions for parameters with defined upper and lower bounds and gamma distributions for parameters defined from zero to infinity) to generate 95% uncertainty ranges around all estimates. We will construct cost-effectiveness acceptability curves, using as a reference South Africa's per-capita gross national income of $5,430 as a willingness to pay per DALY averted[72] but also considering revealed thresholds for potentially competing interventions (e.g., the estimated cost-effectiveness of treatments for MDR-TB for which the government of South Africa has revealed a willingness to pay).

8. **Experiences of inconvenience, attitudes toward confidentiality, motivation to participate, and preferences for disclosure**. Outcome measures will be assessed via Likert scales which will be evaluated via multivariable regression, adjusting for demographic characteristics, district, study arm, and household characteristics (e.g., size). Responses will be dichotomized based on exploratory data analysis and conduct log-binomial regression, comparing these results to those of linear regression performed after assigning a numerical value to each response level. Our generic (e.g. unlabeled) discrete choice experiment (DCE) will be based on five different attributes (disclosure of index case TB status, routine vs off-peak evaluation, inclusion of routine HIV testing, use of official vs unmarked cars, provision of monetary reimbursement for time), each with two different levels. The DCE will utilize a fractional factorial design created to estimate the main effects alone. Results from the DCE for certain characteristics

will be compared against a double-bounded contingent valuation survey in which we will evaluate participants' willingness to accept household CI (with different characteristics) with and without monetary reimbursement of different levels (to compensate for household members' time).

11.5 Blinding

The US-based PI (David Dowdy), the South African-based co-PIs (Neil Martinson and Khatija Ahmed) and NIH sponsors will be blinded to all primary and secondary outcomes during conduct of the study through the completion of data cleaning and analysis.

12 ACCESS TO SOURCE DATA/DOCUMENTS

Research records for this study will be kept in a centralized study office in each district, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a DMID-funded, study, each site will permit authorized representatives of the funder, DMID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Details on all quality control and quality assurance procedures can be found in the associated DMID approved Clinical Quality Management Plan. The participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The data management center will be maintained by PHRU with input from Setshaba Research Centre, and will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database within 2 days of mobile data capture. Cyclical queries will be communicated to the sites for clarification and resolution.

Protocol compliance will be managed on a day-to-day basis by the study coordinator, and overseen by the PI and other study investigators. The study coordinator will ensure proper training on study protocol of all study staff and will conduct routine field visits in order to monitor study compliance. Data quality will be monitored for missing values on a weekly basis by the study coordinator who will review case report forms and remediate errors or omissions with study staff. In depth data quality checks will be made on a quarterly basis, managed by the data manager.

A study monitor from PHRU will make periodic field visits to study sites to review study practices and documents in order to ensure compliance with ethical standards.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonisation Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

14.2 Institutional Review Board

Independent ethics review of this study will be handled in South Africa by the Human Research Ethics Committee at the University of the Witwatersrand, which holds a current U.S. Federal-Wide Assurance issued by OHRP, and in the United States by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

14.3 Informed Consent Process

Written consent (and assent)

Written consent will be obtained for all study participants. For children, written consent will first be obtained from the parent/guardian and followed with written assent from children 7 years and older. Consent will be conducted privately and one-on-one. Consent will be obtained using an easily-understood form (as the educational level of the target population is low). Risks and benefits of participation will be explained, with a clear alternative of no participation, and participants will be clearly informed that consent can be withdrawn at any time without adverse effects on their clinical care. Informed consent will be provided in the participant's preferred language, including English and four local languages (Tshivenda, Sepedi, Tsonga and Setswana). Our experience in Limpopo Province is that, while a number of local dialects are spoken, almost all participants can communicate fluently in one of these languages. All informed consent documents, including a register thereof, will be maintained in a locked cabinet accessible only to study personnel. We anticipate that some of the participants are not literate, and hence not able to read the written consent. For such participants, we will read the consent document as described above, asking participants to make a mark on a corresponding form (and a witness who is not a member of the study staff to sign the form) after having the opportunity to ask any questions and being given the opportunity to decline enrollment with no adverse consequences on their clinical care. Enrollment of illiterate participants will be important to for proper representation of the study population. For these individuals, again, the scientific benefit increases if we are able to include all potential participants (not only those whom we

could consent with on-site staff), and this activity of screening for TB is already the existing standard of care.

14.3.1 Informed Consent/Assent Process (in Case of a Minor or others unable to consent for themselves)

In the case of minors, aged 7-18 years, we will seek written assent, using a separate form from that used for adults. The assent forms will be written in simpler language the details of the study, study procedures and risks. In addition, we will seek parent/guardian informed consent for the participation of these minors. For children <7 years, we will seek only parental informed consent.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study does not intend to exclude any of these special populations.

14.5 Subject Confidentiality

The risks faced by participants in this study relate to consequences due to breach of confidentiality. Disclosure of any clinical information, including HIV and TB status, could be potentially damaging to the study participants. Household visits by the study team may engender stigma by neighbors. These risks will be minimized by ensuring that all study team members are trained in Good Clinical Practices and re-emphasizing the principles surrounding confidentiality on a regular basis in order to ensure that clinical information is handled with respect and in line with the highest research ethics standards. Recruitment, consent and interview of index cases (or next-of-kin) will be conducted in one-on-one in a private room. Household visits will be conducted using unmarked cars and non-uniformed staff. For safety purposes, household visits will be conducted in teams of at least 2 study staff, who will present identifying badges and ask permission before entering the household.

Confidentiality cannot be assured in the presence of focus-group discussions, however we will take several precautions to maximize confidentiality: 1) Emphasize confidentiality at the beginning and end of focus group discussions; 2) Use of alternative name placards instead of actual participant names; 3) Conduct all individual-based activities (e.g. informed consent, reimbursement) in private. Although we will record focus groups as well as in-depth interviews, these recordings will not use participants' names or other identifiers and will be destroyed once the interviews are transcribed/translated.

All study materials will be kept in locked cabinets when not in use, and the study database and files containing transcribed focus groups and interviews will be password protected and stored on secure servers. All paper-based study data will be stored in locked cabinets in a locked

room. Identifiers will be kept separately from all other study data, and will be coded using a unique study ID. The key for this study ID will likely be kept separately. The database will not contain participant identifiers, and will be password protected and stored on a secure database. Data will be accessed by JHU investigators through the secure online password protected database. All recorded interviews will be stored on a password protected secured hard drive and will be destroyed following completion of transcription/translation.

14.6 Future Use of Stored Specimens

The remainder of any sputum specimens not used for Xpert MTB/RIF and/or liquid culture will be stored at the central NICD laboratory for all those testing Xpert MTB/RIF positive, as well as a subset of 5% of all those testing Xpert MTB/RIF negative. Specimens will be stored at -80C in a locked freezer, and will be identified by study ID only. Specimens will be held for the purpose of future testing using a novel diagnostic test for TB. Specimens will be held for 5 years following the close of enrollment (until 30 March 2027) and will then be destroyed.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Details of study data management can be found in the corresponding Data Management plan. In brief, data collection will be conducted by research assistants, interviewers and study nurses. The study coordinator and data manager will be responsible for routine quality control of the data. The principal investigator and other study investigators will be responsible for periodic data review, generating study materials and reports. Our local partners, the Perinatal HIV Research Unit and the Setshaba Research Centre will be responsible for retaining source documents and records. The PI and investigators will be responsible for data interpretation, analysis, as well as review of tables and listing. Reporting to the sponsor and ethics/IRB committees will be the responsibility of the PI and other investigators.

15.2 Data Capture Methods

We will use handheld mobile devices (phones and/or tablets) in order to collect data for this study. We will utilize REDCap, a secure mobile data collection platform for this purpose. Data from interviews and file reviews can be captured directly on the mobile device and either immediately uploaded to a secure online database, or uploaded later in case a good cellular signal is not available. Data may also be captured on paper forms then later entered into REDCap if mobile devices are not available/functional.

15.3 Types of Data

Types of data collected will include those from chart and record review, participant interviews on above listed outcomes, and qualitative interviews for bioethics sub study.

15.4 Timing/Reports

Data review will occur on a quarterly basis in order to ensure enrollment targets are met, and that inclusion/exclusion criteria are followed. Final data review will take place at the completion of each study phase.

15.5 Study Records Retention

The investigator will maintain records pertaining to this study for a period of 5 years following the close of enrollment. Permission is not required prior to destruction of records.

15.6 Protocol Deviations

We will monitor data on a quarterly basis in order to ensure that there are no deviations from protocol.

Protocol compliance will be managed on a day-to-day basis by the study coordinator, and overseen by the PI and other study investigators. The study coordinator will ensure proper training on study protocol of all study staff and will conduct routine field visits in order to monitor study compliance. Additionally, he will review consent forms and study case report forms to identify potential areas for protocol violation, and conduct retraining as necessary. The study PI and other investigators will make period study monitoring visits to ensure protocol adherence, and will conduct weekly teleconference calls with the study coordinator to review progress and address protocol issues in a timely fashion. Likewise, the study coordinator will monitor day-to-day compliance with ethical standards through training, review of practices, consents, enrollment logs and case report forms, as well as through periodic unannounced field visits. Additionally, study monitors from our local partners, the Perinatal HIV Research Unit and Setshaba Research Centre, in South Africa will make periodic field visits to review study practices and documents in order to ensure compliance with ethical standards.

16 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal, as well as present finings at international scientific conferences. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. We will register this trial at ClinicalTrials.gov.

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