PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Ingrid Bassett, MD, MPH

PROTOCOL TITLE
Test and Treat TB: A Proof of Concept Trial in South Africa

FUNDING
National Institute of Allergy and Infectious Diseases

VERSION DATE
5/26/2017

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

We will formally evaluate the value of using a rapid TB screening tool, Xpert MTB/RIF, on the iThembalabantu Tester, a mobile HIV testing unit operating in the peri-urban communities around Durban, South Africa. We will compare the Usual Care to a "Test & Treat TB" (T&T TB) approach. T&T TB includes: i) Xpert MTB/RIF screening on the mobile unit with rapid receipt of test results; ii) expedited TB treatment initiation at the mobile unit; iii) monthly SMS appointment reminders; and iv) cashless incentives. In a 2-arm design, we will compare: 1) T&T TB and 2) Usual care (sample taken at mobile unit and sent for testing at a hospital). We propose a proof-of-concept pilot evaluation to accomplish the following aims:

Aim 1: To establish the feasibility, yield, and clinical impact of a "Test & Treat TB" strategy on a mobile HIV screening unit in South Africa.
Hypothesis: Provision of convenient rapid TB test results with expedited treatment initiation, combined with SMS reminders, will substantially improve rates of TB treatment completion.

Aim 2: To assess the cost and cost-effectiveness of this mobile, integrated HIV/TB screening strategy for maximizing linkage to TB care and treatment completion.
Hypothesis: Viewed from a societal perspective, a T&T TB strategy will be very cost-effective compared to both expedited testing alone and usual care.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

South Africa has the third highest TB incidence in the world, and HIV-infected patients in South Africa entering antiretroviral therapy (ART) programs have a TB prevalence of 20-25%. TB co-infection is associated with a two-fold increased mortality risk and is the leading cause of death. A critical barrier to combating TB in HIV-infected individuals has been the difficulty in securing a rapid, accurate TB diagnosis. The delay in TB case detection leads to increased morbidity and mortality as well as a longer period of infectiousness and increased transmission. Integrating HIV and TB services has been made a priority since ART both reduces the incidence of TB dramatically and improves survival. Interventions that increase efficiency of services have improved linkage to and retention in HIV care, and similar strategies are needed for TB. This project addresses that need by implementing Xpert at the point of care in the community, outside of healthcare facilities, where high-risk individuals may present earlier in the course of TB disease. Bolstered by improvements in ART initiation rates through point of care CD4 testing and theoretical framework of the HIV Test and Treat approach, we will assess the impact of community-based TB diagnosis with Xpert MTB/RIF and expedited treatment initiation on TB outcomes, both at the individual level, with this proof-of-concept clinical trial, and at the population level using mathematical modeling.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

We anticipate 16 months of enrollment to identify 150 TB cases (75/strategy * 2 strategies) who will be eligible to meet the study outcomes. All eligible adults undergoing HIV or TB testing at the iThembalabantu Tester or with the iThembalabantu home testing team will be eligible for enrollment. All subjects who are either HIV-infected or TB symptomatic will be eligible for TB screening with Xpert MTB/RIF.

Inclusion criteria:

1) Age ≥ 18 years
2) English or Zulu speaking
3) Able and willing to give informed consent
4) Willing to share HIV/TB results with study staff
5) Access to mobile phone
6) Willing to attend one of eight local clinics for treatment

Exclusion criteria:

1) Currently taking TB treatment

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Patients waiting to have an HIV or TB test at the mobile unit will be approached a bilingual research assistant (English/Zulu) to assess their interest in study participation. The research assistant will go through a short screening questionnaire with interested and eligible individuals and collect basic demographic information. South African Identification Numbers will be collected by the mobile unit staff. Study participants will provide written informed consent in their primary language. As per usual practice, a Tester staff member will administer a brief questionnaire regarding prior HIV testing history, TB diagnosis and treatment history, TB symptoms, hypertension, and diabetes symptoms. The study team collects these questionnaires from the Tester staff at the end of the day to record the data. Study participants will be asked to provide their mobile phone number and the phone number of a friend or family member, as well consent to later contact by the study team. To assist with follow-up, the research assistant will record the name of the clinic where the patient anticipates receiving HIV and/or TB treatment, in case of a positive HIV test and/or Xpert MTB/RIF test. Patients then undergo rapid HIV testing as per South African protocol, and HIV-infected participants will be offered a point of care CD4 count (Alere PIMA™ Analyzer). Patients can refuse the HIV test and still participate in the TB testing portion of the study if they are TB symptomatic. As per usual practice, all HIV-infected subjects will be given a referral letter by mobile unit staff detailing next steps for HIV treatment, including locations of ART/TB treatment sites. A small group of patients will be recruited through iThembalabantu clinic's home testing team, which works in conjunction with a community-based organization in Umlazi to conduct door-to-door testing and screening for HIV and TB symptoms. A research assistant and study nurse will accompany the home testing team and will assess interest in study participation amongst patients who agree to home testing. Patients recruited via the home testing team will be subject to the same recruitment, study, and follow-up procedures as patients tested directly on the mobile unit.

Participants will be randomized into one of two intervention groups: Usual Care or T&T TB. Randomization will be determined by day, stratified by mobile sites, in blocks of variable sites. All patients seen at the mobile unit or in the home on a given day will be enrolled in the same strategy to simplify logistical considerations and minimize the risk of subjects interacting with subjects in another study strategy.

Participants assigned to Usual Care will provide a sputum sample at the mobile unit or within their home (if being tested by the home testing team) if their TB symptom screen and/or HIV test are positive. They will not undergo Xpert screening on the mobile unit. The sputum sample will be sent by the mobile staff to a hospital for TB testing and positive patients will be contacted as per usual South African protocol. Sputum samples provided by participants assigned to Usual Care who are being tested at home will be sent to the district hospital for TB testing.

HIV-infected or TB symptomatic participants assigned to the T&T TB intervention will receive: mobile unit Xpert MTB/RIF screening and an SMS stating the test results. If TB-positive, they will have the opportunity to receive positive Xpert results at the mobile tester and TB treatment starter pack given at the mobile tester. Patients who return to the tester for the results will be give 20ZAR of cell phone minutes. Those who are tested by the home testing team will not receive Xpert MTB/RIF screening on the mobile unit because the Xpert machine is difficult to transport and requires a constant power source. Instead, sputum samples will be taken to iThembalabantu and the GeneXpert will be run there. Results will be available to home-tested patients within 24 hours via SMS. Patients will receive monthly SMS reminders for appointments for TB care to improve linkage to and retention in clinical care. When a patient makes their first visit to a clinic for TB care, he or she will receive 30ZAR of cell phone minutes. When study staff verify a patient has finished 6 months of TB treatment, the patient will be sent 50ZAR of cell phone minutes by the research project manager.

We will assess linkage to TB and/or HIV care for all participants with a positive Xpert MTB/RIF test regardless of study arm assignment. Three weeks after the mobile unit or home visit, a research team member will contact the TB T&T patient's specified clinic to ascertain whether the patient attended the first TB and/or HIV visit and to obtain the patient's TB registration number. If a patient in the intervention arm did not link to care, the team member will call the patient to encourage him or her to seek care. For patients in the usual care arm, research staff will determine at three weeks whether the patient is TB positive by finding the patient's test results in the National Health Laboratory Services (NHLS) database. For both arms, the team member will also contact clinics at six months to assess retention in care, using the TB registration number and South African ID number as identifiers. A six-month period permits TB-infected individuals to link to a TB clinic and complete TB therapy. [redacted]

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

This study will be conducted at the iThembalabantu Tester, which serves a peri-urban area in Durban, South Africa. A small group of patients will be recruited through iThembalabantu clinic's home testing team, which works in conjunction with a community-based organization in Umlazi to conduct door-to-door testing and screening for HIV and TB symptoms. One of the intervention groups is Usual Care, and the other strategy (T&T TB) will be compared against Usual Care. These strategies are informed by South African Department of Health recommendations.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The study team will obtain approval for all study components from not just the MGH Institutional Review Board but also from the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (Durban ethics board). The approval from UKZN will be submitted to the MGH IRB as soon as it is received.

Potential risks of participation in this study are minimal to moderate and may include stress or anxiety due to new disclosure of HIV status, mild discomfort from having sputum induction, breach of confidentiality, and risk of untreated TB.

The risk of stress and anxiety due to discussion about HIV, TB, HIV and TB screening, and disclosure of HIV status will be minimized by conducting all discussions in a private space. Patients will be informed that their responses to questions will in no way affect their care at the mobile unit and that subsequent care providers will not have access to their answers. The research assistant will start each interview by reminding respondents that they are free to decline to answer any question. None of the information collected through this investigation could affect a subject's relationship with other individuals, such as patient-physician or family relationships, or impact the subject's HIV or TB treatment at other sites.

Study subjects' privacy will be protected. As is typical for clinical settings, patients will be offered a private place to undergo the baseline questionnaire and consent. Accompanying family members or friends will be asked to wait elsewhere. Any phone conversations after enrollment will be conducted with patients only when they are comfortable and can speak freely. SMS messages will be specific and informative about the patient's TB results and the subsequent steps in TB care the patient needs to take; a patient's HIV status will never be mentioned in an SMS. TB carries significantly less stigma than HIV and to prevent serious misunderstandings and miscommunication due to vague messages, SMS messages will be specific to TB. Clear, informative messages will also be more helpful to patients because they will

not be confused by a generalized message. [redacted]

Risks will also be minimized by handling all research data in a confidential manner. The research office is [redacted] sealed with a password-protected electronic entrance and does not include patient care areas. To assure confidentiality, each subject will receive a unique identification number. Research data and entry forms will be labeled only with this number. The research team in Durban will maintain a locked file cabinet in the research office accessible only to the project manager that connects patient identifiers to unique identifiers. This information will not be available to the Partners-based investigators. Participant confidentiality will be protected through the use of study numbers, rather than unique identifiers, at the time of analysis.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Subjects will be free to withdraw voluntarily from the study at any time. The evaluation team will start each interview by reminding respondents that they are free to decline to answer any question they find difficult or uncomfortable. To maximize patient safety and public health, subjects in the TB T&T arm who have not linked to care at the time of the first follow-up assessment (3 weeks after testing) will be considered to have failed to reach the secondary study outcome of linkage to care, defined as the first clinic visit. Because patients in the usual care arm will receive a call from a local TB nurse about their results, we will not have any further contact with patients in the usual care arm. We will follow-up on patient outcomes in the usual care arm at 9 months by contacting the patient's self-identified clinic and looking up the patient on South Africa national databases.

In addition, standard protocols to protect the confidentiality of the data will be followed. All aggregate data will be securely stored either in locked file cabinets or, if in electronic form, on password-protected computers equipped with anti-virus software. All subjects will be followed for the duration of the study unless they choose to withdraw from the study.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Potential risks of participation in this study are minimal to moderate and may include stress or anxiety due to new disclosure of HIV status, mild discomfort from having sputum induction, breach of confidentiality, and risk of untreated TB.

Stress and anxiety due to disclosure of HIV status:
Subjects have presented to the iThembalabantu tester or consented to a home visit from the iThembalabantu home testing team and agreed to undergo an HIV test, and therefore the mild pain from the finger-prick test is going to be incurred regardless of the study. All HIV testing is ultimately voluntary, and patients can choose not to test at any time. The questionnaires used for data collection should not cause psychological stress.

We anticipate that some patients who are diagnosed with HIV infection during the course of the study will experience additional fear and anxiety in dealing with their new diagnosis. The Tester has trained counselors available to discuss test results with patients and has access to an appropriate, easily-accessible social work department that has a strong focus on HIV-related issues.

Though this anxiety will be faced by many patients, most HIV-infected patients will eventually be diagnosed with their disease through the course of progressive immunosuppression. Thus, this anxiety is most likely inevitable. The literature suggests that the improvements in life expectancy and quality of life benefits associated with earlier diagnosis and care will exceed the transient anxiety associated with the initial diagnosis.

Discomfort of sputum induction for TB testing:
Patients who agree to TB screening and require sputum induction may experience slight irritation from the induction of sputum using hypertonic nebulized saline. The saline is mildly irritating, but rapidly, within minutes, will often generate a cough forceful enough to produce a sputum specimen. Each induction uses a fresh, single-use tubing for the nebulizer to avoid cross-infection. Sputum collection will follow local infection control practices, including collection of sputum in an outdoor area separate from patient waiting areas.

Breach of confidentiality:
It is extremely important that study subjects' privacy is protected. As is typical for clinical settings, patients will be offered a private place to undergo

the baseline questionnaire and consent. Accompanying family members or friends will be asked to wait elsewhere. Participants' HIV status is kept in a locked cabinet in the iThembalabantu research office that will be accessed by the research staff to document study subjects' test results only when no patients are present. All study forms will be kept in locked file drawers, available at the South African site. All aggregate data will be securely stored either in locked file cabinets or, if it electronic form, on password-protected computers equipped with anti-virus software.

Patients recruited via the home testing team will also be ensured privacy during home visits. The home testing team goes into homes to screen for a number of conditions, including HIV, TB, hypertension, and diabetes. The team also inquires about vaccinations in children and assesses if pregnant women in the household are in need of antenatal care. This broad range of services helps to ensure that people are not specifically targeted for HIV testing. Additionally, these teams are well-known to the community and routinely make home visits, which helps to normalize their presence. The home testing team keeps all patient records confidential and visits all of the households in a catchment area to avoid stigmatizing any individual household.

Any phone conversations after enrollment will be conducted with patients only when they are comfortable and can speak freely. SMS messages will be specific to TB and not have any mention of HIV.

Risk of untreated TB for subjects not linked to care:
Some subjects will get a diagnosis of TB during the course of the study. To maximize patient safety and public health, subjects in the TB T&T arm who have not linked to care at the time of the first follow-up assessment (3 weeks after testing) will be contacted by research staff. Because the South African standard of care for TB positive patients involves calling patients, we will not contact these patients separately.

Subjects newly diagnosed with TB in the T&T TB strategy will be given a two-week TB treatment starter pack with a label indicating that this is the only the start of a longer treatment course, along with extensive counseling related to the importance of seeking further care at their clinic, the need for at least 6 months of TB treatment, and an SMS reminder near the end of the starter pack. The provision of a weight-based, fixed dose combination starter pack is typical practice at the time of new TB diagnosis in non-Department of Health TB treatment sites in South Africa.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the

treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Individual patients in the study, regardless of what strategy to which they are assigned, will benefit from their participation by being tested for TB with rapid, newly-available tests if they are at high risk of TB (HIV-infected or have TB symptoms), which will allow subjects to receive a diagnosis of TB more quickly. TB testing can help people get the care that they need and help them live longer. Detection and treatment of TB also has the potential benefit of decreasing transmission to others in a patient's environment.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Subjects for this analysis will be recruited from mobile HIV testing sites in and around Umlazi Township in KwaZulu-Natal. A small group of patients will be recruited through iThembalabantu clinic's home testing team. Subjects will have presented to these sites voluntarily or agreed to a home visit by the iThembalabantu team. All eligible adult patients will be offered enrollment. The distribution of gender and age will reflect the current mobile testing population. Women known to be pregnant will be encouraged to seek care to ensure adequate prenatal care. While HIV infection is an important problem in children, analysis of an intervention to improve linkage to HIV and TB care for children is beyond the scope of this pilot project. Children diagnosed with HIV are aggressively linked to care by study sites by being immediately taken to the HIV clinic even without a CD4 cell count, unlike adult patients. Additionally, the mobile testing unit does not test children under 15 years of age, and those ages 15-17 typically present alone or with an informal caretaker who would be unable to provide informed consent because they are not the legal health care proxy or guardian according to South African policies regarding non-therapeutic research trials.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Individuals who speak either English or Zulu will be eligible for participation in this study.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

All subjects will be recruited from the iThembalabantu mobile HIV testing unit operating in the peri-urban communities around Durban. A small group of patients will be recruited through iThembalabantu clinic's home testing team, which works in conjunction with a community-based organization in Umlazi to conduct door-to-door testing and screening for HIV and TB symptoms. The subjects will be approached by a bilingual research assistant (English/Zulu) prior to undergoing an HIV test. The research assistant will ascertain the patient's eligibility based on a screening questionnaire, will describe the study, answer any questions, and invite the patient to participate. At this contact, conducted in English or Zulu, depending on patient preference, the research assistant will describe the risks, benefits, and alternatives, including non-participation. Patients who agree to participate and can fully comprehend the study will sign a written consent form in their language of choice. They will then undergo a questionnaire prior to HIV testing.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Participants randomized to the intervention arm can receive a small cashless incentive of up to 100 ZAR (equivalent to 9 US dollars) of cell phone minutes. TB-positive patients can receive 20 ZAR for picking up their results at the mobile unit, 30 ZAR for linking to care at a clinic, and 50 ZAR for completing TB treatment.

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Most subjects will be recruited from the iThembalabantu mobile HIV testing unit operating in the peri-urban communities around Durban. A small group of patients will be recruited through iThembalabantu clinic's home testing team, which works in conjunction with a community-based organization in Umlazi to conduct door-to-door testing and screening for HIV and TB symptoms. The subjects will be approached by a bilingual research assistant (English/Zulu) prior to undergoing an HIV or TB test. The research assistant will ascertain the patient's eligiblity based on a screening questionnaire, will describe the study, answer any questions, and invite the patient to participate. At this contact, conducted in English or Zulu, depending on patient preference, the research assistant will describe the risks, benefits, and alternatives, including non-participation. Patients who agree to participate and can fully comprehend the study will sign a written consent form in their language of choice. They will then undergo a questionnaire prior to HIV or TB testing. As is typical for clinical settings, patients will be offered a private place to undergo the baseline questionnaire and consent. Accompanying family members or friends will be asked to wait elsewhere.

Patients will be informed that their responses to questions will in no way affect their care at the mobile unit and that subsequent care providers will not have access to their answers. The research assistant will start each interview by reminding respondents that they are free to decline to answer any question. None of the information collected through this investigation could affect a subject's relationship with other individuals, such as patient-physician or family relationships, or impact the subject's HIV or TB treatment at other sites.

The mobile testing unit moves from place to place without a publicly available schedule. Therefore, patients presenting for HIV or TB testing on any given day will not be aware of the research study in advance, and they will not have an extended amount of time in which to make the decision to participate.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

A Data Safety and Monitoring Board (DSMB) will be developed, which will consist of three independent reviewers, including a statistician, an expert in HIV/TB, and a clinician. The DSMB will meet once every six months by conference call. The Principal Investigator will prepare material for the DSMB to review and will not be present for part of the DSMB meeting. The DSMB will be provided with reports of adverse events as they occur, and the Chair of the DSMB has the responsibility of calling an ad hoc meeting if the type or frequency of serious adverse events is of concerns. The DSMB may request additional information from the Principal Investigator at any time in the course of its review of the study. The DSMB will ensure documentation of informed consent and review confidentiality procedures. A report will be provided to the Principal Investigator, the University of KwaZulu-Natal Ethics Committee, and the Partners Human Research Committee. The DSMB will cease meeting after enrollment concludes.

Data monitoring and quality assurance will be done on an ongoing basis. A project coordinator and data coordinator will monitor study data every month to ensure the accuracy and completeness of consent forms and other study questionnaires. In order to ensure patient safety, data and safety

monitoring will include review of all adverse events, enrollment, and protocol deviations, in addition to review of any interim analyses to ensure confidentiality is maintained. Field staff will be responsible for reporting adverse events, including breach of patient confidentiality, to the project coordinator, local Co-Investigator, and the Principal Investigator.

Adverse events and unanticipated problems that occur during the conduct of the study, after study completion, or after subject withdrawal or completion will be submitted within 5 working days/7calendar days of the date that the Principal Investigator first becomes aware of the problem, as per the Partners Human Research Committee's policy.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Data monitoring and quality assurance will be done on an ongoing basis. A project coordinator and data coordinator will monitor study data every month to ensure the accuracy and completeness of consent forms and other study questionnaires. In order to ensure patient safety, data and safety monitoring will include review of all adverse events, enrollment, and protocol deviations, in addition to review of any interim analyses to ensure confidentiality is maintained. Field staff will be responsible for reporting adverse events, including breach of patient confidentiality, to the project coordinator, local Co-Investigator, and the Principal Investigator.

The DSMB will be provided with reports of adverse events as they occur, and the Chair of the DSMB has the responsibility of calling an ad hoc meeting if the type or frequency of serious adverse events is of concerns. The DSMB may request additional information from the Principal Investigator at any time in the course of its review of the study. The DSMB will ensure documentation of informed consent and review confidentiality procedures. A report will be provided to the Principal Investigator, the University of KwaZulu-Natal Ethics Committee, and the Partners Human Research Committee.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

Data monitoring and quality assurance will be done on an ongoing basis. A project coordinator and data coordinator will monitor study data every month to ensure the accuracy and completeness of consent forms and other study questionnaires. In order to ensure patient safety, data and safety monitoring will include review of all adverse events, enrollment, and protocol deviations, in addition to review of any interim analyses to ensure confidentiality is maintained. Field staff will be responsible for reporting adverse events, including breach of patient confidentiality, to the project coordinator, local Co-Investigator, and the Principal Investigator.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/guidance.htm#13

Reporting Unanticipated Problems (including Adverse Events)
http://healthcare.partners.org/phsirb/guidance.htm#7

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All study sites have internet access and the capacity to enter computerized data. The Partners-based investigators will work closely with the South

African team on all data collection and management systems. Trained research assistants will record participant responses on paper data forms. Data collection forms will be scanned and uploaded weekly. Original forms will be kept in a locked cabinet in a locked office. The research office is [redacted] password-protected electronic entrance and does not include patient care areas. Screening and enrollment data will be entered locally by dedicated, trained staff into a web-based study tracking system, which will be constructed and maintained by the Partners-based team. All data transmissions will be encrypted. Local workstations and networks are password-protected and restricted to use by study personnel only.

Adherence to confidentiality measures will be overseen on site by the study project manager. All data will be collected by the South African team, and each participant will receive unique study ID number. Research data and entry forms will be labeled only with this number. The research team in Durban will maintain a locked file cabinet in the research office accessible only to the project manager that connects patient identifiers to unique identifiers. This information will not be available to the Partners-based investigators who will have access only to data stripped of patient identifiers. Participant confidentiality will be protected through the use of study numbers, rather than unique identifiers, at the time of analysis.

The risk of stress and anxiety due to discussion about HIV, TB, HIV and TB screening, and disclosure of HIV status will be minimized by conducting all discussions in a private space. Patients will be informed that their responses to questions will in no way affect their care at the mobile unit and that subsequent care providers will not have access to their answers. The research assistant will start each interview by reminding respondents that they are free to decline to answer any question. None of the information collected through this investigation could affect a subject's relationship with other individuals, such as patient-physician or family relationships, or impact the subject's HIV or TB treatment at other sites.

Study subjects' privacy will be protected. As is typical for clinical settings, patients will be offered a private place to undergo the baseline questionnaire and consent. Accompanying family members or friends will be asked to wait elsewhere. Any phone conversations after enrollment will be conducted with patients only when they are comfortable and can speak freely. SMS messages will be specific to TB and not have any mention of HIV.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent,

and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No data will be collected by Partners investigators as part of this study. All data will be collected by the South African team.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

All data will be collected by collaborators in South Africa. Specimens used for Xpert MTB/RIF screening will be disposed of appropriately. Specimens used in the validation process will be sent to the National Health Laboratory Service (NHLS) for microscopy and culture. Specimens will not be stored.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

The research team in Durban will collect and maintain the study data, and the Partners-based investigators will only have access to data stripped of patient identifiers, which will be sent by encrypted transfers. The South Africa-based project manager will be the only individual will access to the locked file cabinet containing the linkages to patient identifiers.