## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The Tuberculosis Sentinel Research Network (TB-SRN) of the International epidemiology Databases to Evaluate AIDS (IeDEA): protocol for a prospective cohort study in Africa, Southeast Asia, and Latin America |
| **AUTHORS** | Enane, Leslie; Duda, Stephany N.; Chanyachukul, Thida; Bolton-Moore, Carolyn; Navuluri, Neelima; Messou, Eugène; Mbonze, Nana; McDade, LaQuita R.; Figueiredo, Marina Cruvinel; Ross, J; Evans, Denise; Diero, Lameck; Akpata, Robert; Zotova, Natalia; Freeman, Aimee; Pierre, Marie Flore; Rupasinghe, Dhanushi; Ballif, Marie; Byakwaga, Helen; de Castro, Nathalie; Tabala, Martine; Sterling, Timothy; Sohn, Annette; Fenner, Lukas; Wools-Kaloustian, Kara; Poda, Armel; Yotebieng, Marcel; Huebner, Robin; Marcy, Olivier |

## VERSION 1 – REVIEW

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| **REVIEWER** | Houben, Rein<br>London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology |
| **REVIEW RETURNED** | 25-Sep-2023 |

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| **GENERAL COMMENTS** | This is a very useful study, which looks to leverage an existing network to enrich the data and knowledge landscape around post-TB. That is welcome. However, there are a number of areas where a little more discussion would provide a lot more value to the field, by enabling the wider field to understand what direction the team is taking.<br>Below I've highlighted a number such areas, which I hope the authors find useful to reflect on.<br>The study will need to be able to stratify between bac confirmed and clinically diagnosed individuals, as the definition of clinically diagnosed will vary between settings, and with it disease severity? Agree it is a strength to reflect the global TB survivor population, but will need to take this into account. The criteria for clinical diagnosis are not described, nor is it clear how they are harmonised across the many recruiting sites.<br>Re measurements: While the measurements are clear and well-described, it is not clear if these have clinical relevance for post-TB (e.g. SGRQ), and the analysis plan would benefit from some reflections on how this affects the analysis and interpretation.<br>The abstract suggests the study will collect sociodemographic factors, but this seems limited to the initial visit, suggesting sociodemographic measures are only considered an exposure, not a potentially modifiable post-TB outcome. That would seem a missed opportunity given how important SES outcomes are in TB. I would suggest the team make more clear how they will use SES, and why they can not extend this to e.g. 12m post TB. |

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| | Patient sampling/recruitment is not clear – are these simply consecutive patients, or purposively sampled? If the latter, how? Pg13/l11 suggests there is a target for overall HIV prevalence across the sites, but more clarity is needed.<br>Box 1 is a bit strange on its own and I don't know how to interpret it or what it adds. E.g. how is 'youth life stage (ages 15-24)' an area of investigation? Would suggest explaining it better, or drop.<br>In addition, the sample size calculations are a bit too high level. Given the number of potential strata of interest (15-24 vs older, HIV/not HIV, bac confirmed/clin diagnosed), it would be useful to consider how many of each group are expected to be found and what prevalence/incidence of e.g. PTLD or recurrent TB is expected in each group, and then calculate power to detect a prevalence within a group and/or difference between groups.<br>Overall, it is not clear what the study or analysis outcomes are. Is it looking to identify the prevalence or incidence of this set of post-TB outcomes in this cohort, is it to describe relative prevalence or incidence, and if so, will a composite outcome be used, or simply a 'yes/no' outcome, or how will such an analysis be done? Currently this area is very light or almost completely lacking in detail. As it stands, this is more a description of what data will be collected, without a clear (enough) purpose. It would benefit a lot (and be a more useful contribution to the growing literature around post-TB) if more details were provided. |

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| **REVIEWER** | Hertzmark, Ellen<br>Harvard University T H Chan School of Public Health, Global Health |
| **REVIEW RETURNED** | 29-Sep-2023 |

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| **GENERAL COMMENTS** | I congratulate the authors for putting together this ambitious study. This is a really good start for what can be a really important study. Both the commonalities and the differences among sites will be important for hypothesis generation.<br>Who will be funding this study?<br>I know that the diagnosis of TB is often difficult. I also know that proposals are often written with wildly optimistic assumptions about how long it will take to recruit the desired number of patients. It seems likely that at least one site will trail the others. There should probably be a plan of what to do in such a case.<br>For purposes of gauging the generalizability of the study, it will be important to keep records of at least some basic characteristics of those initially screened who do not end up in the study, at least age and sex, reason for ineligibility (if relevant), unwillingness to be tested for HIV, or nonconsent for the study.<br>I did not see a power or sample size calculation. I suppose that this relates to their statement that the proposed study is merely "descriptive," but the urge to do statistical testing is usually very strong. Perhaps the sample sizes are determined by what the authors think they can get in a reasonable time (not specified—but it should be). In any case, perhaps some idea of minimum detectable differences/risk ratios would be helpful. Given that it is rare for studies to recruit all the eligible patients, and that the eligible patients are some unknown fraction of all patients, some justification of the numbers for each site would be helpful.<br>There seems to be at least some seasonal aspect to TB incidence (or perhaps better, TB diagnosis), which might or might not relate to HIV, success of therapy, and other factors. This study is probably not the study to figure that out, but there is some possibility that the wide geographic distribution, obviously one of |

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| | the proposed study's great virtues, will somehow obscure some aspect of TB and TB treatment and their relation to HIV because of different timing of seasons in the 11 countries.<br>Since the numbers at the individual sites are small, it will be difficult (i.e., low power) to tease out effects based on either local characteristics or on specifics of local management. Also, I assume that the sites will vary widely in the fraction of TB cases that are coinfected with HIV. It also seems likely that many HIV diagnoses will be made as a result of referrals from the TB clinic (and vice versa). I wonder a bit about the quality of the HIV data that will be available from "routine care." It is also not clear how people who are newly infected with HIV during the follow-up period or people who become pregnant during the follow-up period will be treated (?split time?). Often people who are in routine care for one condition or disease are more likely to have a second condition or disease found, simply because they are being seen more often.<br>I assume that some of the sites are rural and some urban. I hope the study will take this fact, as well as sex and age, into account.<br>What will happen to the (unfortunately, presumably many) patients who stop TB therapy or stop coming to the clinic? Or, presumably, the coinfected patients who stop their HIV treatment?<br>Perhaps I missed this, but where are the proposed data-gathering forms? Shouldn't they be in a supplement? In general, the methodological aspects of the study are not sufficiently specified.<br><br>Specific Comments<br>page line<br>1 9 45-46 "PTLD" is used without having been defined (the first place I see is page 16, line 10).<br>2 12 14-15 What is "concept driven analysis?"<br>3 14 41-45 Are these histories from the patient or from their medical records? Please clarify in the text.<br>4 48-49 Please be specific about the "Specific information" relevant to youth.<br>5 14/53-15/8 Even assuming that all these instruments are widely validated, it is likely that there are locally applicable cutoffs or interpretations. How do they plan to treat this issue?<br>6 15 30-31 Is this an exhaustive list of all the languages? Have all the translations been tested and validated? If not yet, will they be?<br>7 16 bottom of table Has LLN been defined? I assume it means "lower limit of normal." Is "normal" defined by country/site or globally for all sites? Perhaps there is a WHO definition that I (as a statistician not working in this area) am not aware of.<br>8 19 51-52 or, HIV could modify/moderate the effects of some treatments.<br>9 54-56 So they expect about 430 "youth with TB" in the study. This seems like a reasonable sample size, and if their description of the current state of knowledge is accurate, something is way better than almost nothing.<br>10 20 24-25 The "strict protocols…data" should be described. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1

1) "The study will need to be able to stratify between bacteriologically confirmed and clinically diagnosed individuals, as the definition of clinically diagnosed will vary between settings, and with it disease severity? Agree it is a strength to reflect the global TB survivor population, but will need to

take this into account. The criteria for clinical diagnosis are not described, nor is it clear how they are harmonised across the many recruiting sites."
We agree with the Reviewer that these details would be helpful and have included the definitions, as specified in the TB-SRN study protocol.

METHODS AND ANALYSIS. Study design: Paragraph 1 (added):
Clinically diagnosed pulmonary TB is defined by clinical diagnosis by medical providers through standard of care, in the absence of confirmatory testing, prompting initiation of TB treatment. Specific eligibility criteria that must be met as part of clinical diagnosis include having either (1) any signs or symptoms of active TB (e.g., persistent cough, hemoptysis, fever, unintended weight loss, fatigue or lethargy, night sweats, pleuritic chest pain) together with chest X-ray findings consistent with pulmonary TB, or (2) presence of respiratory signs and symptoms (including chronic cough, hemoptysis, or pleuritic chest pain) regardless of chest X-ray findings.

2) "Re measurements: While the measurements are clear and well-described, it is not clear if these have clinical relevance for post-TB (e.g. SGRQ), and the analysis plan would benefit from some reflections on how this affects the analysis and interpretation."
We appreciate this comment. We have added further description of our consideration of post-TB assessments, including details regarding previous validation and use of the SGRQ in studies of individuals treated for pulmonary TB.

METHODS AND ANALYSIS. Outcome measures: Paragraph 3:
Post-treatment outcomes to be ascertained are informed by emerging research surrounding post-TB sequelae.27 40 43 Post-TB lung disease will be defined by new, recurrent or persistent respiratory symptoms or signs that occur post-treatment; hypoxemia (oxygen saturation <90%); pulmonary function impairment; or chest X-ray abnormalities.40 Spirometry definitions for pulmonary function impairment include the following: forced expiratory volume in one second (FEV1) / Forced vital capacity (FVC) ratio < lower limit of normal (LLN), FEV1 <LLN, and/or FVC <LLN. Global Lung Function Initiative (GLI) standard reference equations will be used to calculate LLN (fifth centiles) for each participant; these will be compared with observed values.41 42 Functional status will be assessed with one-minute sit-to-stand testing. Further measures of well-being after TB treatment will include symptoms of depression (by PHQ-9)28 and health-related quality of life (by SGRQ).31 32 The SGRQ has previously been validated31 and applied in studies of individuals treated for pulmonary TB.44-49 Both the PHQ-9 and SGRQ are among the assessments recommended by some experts for the evaluation of post-TB sequelae.27

3) "The abstract suggests the study will collect sociodemographic factors, but this seems limited to the initial visit, suggesting sociodemographic measures are only considered an exposure, not a potentially modifiable post-TB outcome. That would seem a missed opportunity given how important SES outcomes are in TB. I would suggest the team make more clear how they will use SES, and why they can not extend this to e.g. 12m post TB."
We agree that longitudinal sociodemographic data would be of interest, but data collection beyond the baseline was limited by site capacities and funding. However, as part of regionally driven sub-studies, TB-SRN sites in East Africa are collecting SES outcomes at later timepoints and intend to conduct additional analyses evaluating select social and economic outcomes of TB treatment. These data will be used to inform future research that emerges from the TB-SRN study.

4) "Patient sampling/recruitment is not clear – are these simply consecutive patients, or purposively sampled? If the latter, how? Pg13/l11 suggests there is a target for overall HIV prevalence across the sites, but more clarity is needed."

We confirm that we will use consecutive enrollment, as described in the “Study Design” section. We have clarified that we anticipate 20-30% HIV prevalence among individuals with pulmonary TB across study sites, in the section regarding “Sample size considerations”.

METHODS AND ANALYSIS. Sample size considerations: Paragraph 1 (revised):
The overall cohort sample size of 2,600 participants will enable precise estimates of key treatment and post-treatment outcomes. Given the anticipated HIV prevalence of 20 to 30% across the global cohort, this sample size will also allow for multivariable analyses, including on HIV co-infection and treatment-related factors, in addition to sex, age, and additional demographic or clinical factors.

5) “Box 1 is a bit strange on its own and I don’t know how to interpret it or what it adds. E.g. how is ‘youth life stage (ages 15-24)’ an area of investigation? Would suggest explaining it better, or drop.
We appreciate the concerns and have removed Box 1.

6) In addition, the sample size calculations are a bit too high level. Given the number of potential strata of interest (15-24 vs older, HIV/not HIV, bac confirmed/clin diagnosed), it would be useful to consider how many of each group are expected to be found and what prevalence/incidence of e.g. PTLD or recurrent TB is expected in each group, and then calculate power to detect a prevalence within a group and/or difference between groups.”
We have added further details to our sample size considerations for clarification. Because multiple analyses are planned from this cohort, our sample size is based on similar cohorts and on major outcomes and key independent variables. We recognize that this is a potential limitation as we are not generating separate sample size calculations for each potential research question.

METHODS AND ANALYSIS. Sample size considerations: Paragraphs 1 and 2 (revised):
The IeDEA TB-SRN will enroll 2,600 participants across all study sites, including 300 participants in each of five IeDEA regions (Asia-Pacific, Central Africa, East Africa, Southern Africa, and West Africa), and 1100 participants in CCASAnet. It is estimated that between 5% and 10% of treated TB cases will result in TB treatment failure or TB recurrence. Thus, if 2,600 participants with active TB are enrolled, it is expected that between 130 and 260 episodes of treatment failure or recurrence will occur, with 200 being an approximate midpoint estimate. Furthermore, the majority of recurrent episodes are estimated to occur within 6 months of treatment completion, and thus >90% of all such episodes are expected to be detected during the follow-up period. Pulmonary function impairment may be anticipated in approximately 50-60% of participants after completion of TB treatment.52 The overall cohort sample size of 2,600 participants will enable precise estimates of key treatment and post-treatment outcomes. Given the anticipated HIV prevalence of 20 to 30% across the global cohort, this sample size will also allow for multivariable analyses, including on HIV co-infection and treatment-related factors, in addition to sex, age, and additional demographic or clinical factors.
As the TB-SRN is a descriptive study encompassing multiple planned outcomes and analyses, statistical considerations and power will vary by the research question proposed within the concept process of IeDEA.

7) “Overall, it is not clear what the study or analysis outcomes are. Is it looking to identify the prevalence or incidence of this set of post-TB outcomes in this cohort, is it to describe relative prevalence or incidence, and if so, will a composite outcome be used, or simply a ‘yes/no’ outcome, or how will such an analysis be done? Currently this area is very light or almost completely lacking in detail. As it stands, this is more a description of what data will be collected, without a clear (enough) purpose. It would benefit a lot (and be a more useful contribution to the growing literature around post-TB) if more details were provided.”
We appreciate the concerns noted by the reviewers. As noted above, multiple analyses are planned from this observational cohort study around a range of outcomes. These are described both in the text

and outlined in Table 3 and will be detailed in dedicated concept sheets that correspond to separate research questions. We have revised the text to clarify this point.

METHODS AND ANALYSIS. Data analysis plan: Paragraphs 1 and 2:
While data may be used by the individual TB-SRN sites or regions, they are primarily being collected and harmonized for multiregional research, following IeDEA's standard operating procedures governing research collaboration.50 The TB-SRN observational cohort study is designed to inform multiple analyses. Analyses of global TB-SRN data will be proposed through concept sheets, for detailed review and feedback from collaborators in the TB-SRN and other IeDEA working groups relevant to the study, with subsequent final review and approval by the IeDEA Executive Committee.50 Concepts will center on major research questions in TB and HIV clinical epidemiology.51 These will include analyses of TB severity, TB treatment and post-treatment outcomes including post-TB lung disease, health-related quality of life, and associated clinical, mental health, and life course factors. Youth with TB (ages 15-24) will be assessed as a subset of this cohort, with attention to their clinical, psychosocial, and lung health findings. The subset of pregnant and post-partum participants will also be described, to include specific variables and outcomes in this group.
Current, initial TB-SRN concepts delineate analyses in the following areas: baseline TB severity and associated factors; baseline depressive symptoms and substance use; chronic hypoxemia and respiratory symptoms; and PTLD in youth.

Reviewer 2

1) "Who will be funding this study?"
The study is funded by the U.S. National Institutes of Health. We have added this to the introduction to clarify.

INTRODUCTION: Paragraph 3 (revised):
The Tuberculosis Sentinel Research Network (TB-SRN) is a global platform for coordinated observational TB research within the IeDEA consortium, which receives funding from multiple institutes and centers within the US National Institutes of Health (NIH).

2) "I know that the diagnosis of TB is often difficult. I also know that proposals are often written with wildly optimistic assumptions about how long it will take to recruit the desired number of patients. It seems likely that at least one site will trail the others. There should probably be a plan of what to do in such a case."
We agree with the Reviewer that this is an ongoing challenge with multicenter studies, particularly those conducted in many countries. The first site (in Zambia) began enrollment in September 2022 and the final site (in Thailand) is projected to complete enrollment in October 2024. With other prospective studies conducted in the IeDEA consortium, we have pursued initial analysis using data from sites that have completed enrollment. We expect to do the same in TB-SRN to avoid delaying the reporting of study findings.

3) "For purposes of gauging the generalizability of the study, it will be important to keep records of at least some basic characteristics of those initially screened who do not end up in the study, at least age and sex, reason for ineligibility (if relevant), unwillingness to be tested for HIV, or nonconsent for the study."
We consider that participant cohort demographics may be broadly compared with the aggregate characteristics of registrants in pulmonary TB care, as reported by national TB programs for the respective sites. We additionally confirm that most sites maintain a screening log to collect the characteristics of patients who are not eligible or who decline to participate in the study.

4) “I did not see a power or sample size calculation. I suppose that this relates to their statement that the proposed study is merely “descriptive,” but the urge to do statistical testing is usually very strong. Perhaps the sample sizes are determined by what the authors think they can get in a reasonable time (not specified—but it should be). In any case, perhaps some idea of minimum detectable differences/risk ratios would be helpful. Given that it is rare for studies to recruit all the eligible patients, and that the eligible patients are some unknown fraction of all patients, some justification of the numbers for each site would be helpful.”
We appreciate this suggestion. We have added further details to our sample size considerations. Because multiple analyses are planned from this cohort, our sample size considerations will be based on key outcomes and exposure variables. We recognize that this is a potential limitation as we are not generating separate sample size calculations for each potential research question.

METHODS AND ANALYSIS. Sample size considerations: Paragraphs 1 and 2 (revised):
The IeDEA TB-SRN will enroll 2,600 participants across all study sites, including 300 participants in each of five IeDEA regions (Asia-Pacific, Central Africa, East Africa, Southern Africa, and West Africa), and 1100 participants in CCASAnet. It is estimated that between 5% and 10% of treated TB cases will result in TB treatment failure or TB recurrence. Thus, if 2,600 participants with active TB are enrolled, it is expected that between 130 and 260 episodes of treatment failure or recurrence will occur, with 200 being an approximate midpoint estimate. Furthermore, the majority of recurrent episodes are estimated to occur within 6 months of treatment completion, and thus >90% of all such episodes are expected to be detected during the follow-up period. Pulmonary function impairment may be anticipated in approximately 50-60% of participants after completion of TB treatment.52 The overall cohort sample size of 2,600 participants will enable precise estimates of key treatment and post-treatment outcomes. Given the anticipated HIV prevalence of 20 to 30% across the global cohort, this sample size will also allow for multivariable analyses, including on HIV co-infection and treatment-related factors, in addition to sex, age, and additional demographic or clinical factors.
As the TB-SRN is a descriptive study encompassing multiple planned outcomes and analyses, statistical considerations and power will vary by the research question proposed within the concept process of IeDEA.

5) “There seems to be at least some seasonal aspect to TB incidence (or perhaps better, TB diagnosis), which might or might not relate to HIV, success of therapy, and other factors. This study is probably not the study to figure that out, but there is some possibility that the wide geographic distribution, obviously one of the proposed study’s great virtues, will somehow obscure some aspect of TB and TB treatment and their relation to HIV because of different timing of seasons in the 11 countries.”
We agree that the seasonality of TB incidence or diagnosis could impact the factors noted by the reviewer. Questions related to the effects of increasing extreme weather globally on routine HIV care are a focus of our parent HIV cohort, IeDEA. We note that seasonal patterns may be examined in TB-SRN if data are assessed together with added site-level data or other inputs (e.g. related to the timing of harvest seasons and/or weather patterns or other temporal changes at the site level).

6) “Since the numbers at the individual sites are small, it will be difficult (i.e., low power) to tease out effects based on either local characteristics or on specifics of local management. Also, I assume that the sites will vary widely in the fraction of TB cases that are coinfected with HIV. It also seems likely that many HIV diagnoses will be made as a result of referrals from the TB clinic (and vice versa). I wonder a bit about the quality of the HIV data that will be available from “routine care.” It is also not clear how people who are newly infected with HIV during the follow-up period or people who become pregnant during the follow-up period will be treated (?split time?). Often people who are in routine care for one condition or disease are more likely to have a second condition or disease found, simply because they are being seen more often.”

We agree that the numbers are likely to be too small to identify possible effects of local practices at the level of the individual site. However, we expect to be able to evaluate associations with some site-level characteristics and practices across the cohort. We gather information on site-level characteristics and practices through a separate “Site Assessment” survey administered to IeDEA sites every 2-3 years, discussed further in item (7) below. We have ensured, however, that site and regional differences are mentioned in the study limitations.

We recognize the limitations of routinely collected data. We would note that the global IeDEA consortium has over fifteen years’ experience gathering such data and has implemented data quality checking and auditing activities to optimize the quality data and undertake a number of data harmonization efforts to streamline data management (see Lotspeich et al. “Lessons learned from over a decade of data audits in international observational HIV cohorts in Latin America and East Africa," in press with Journal of Clinical and Translational Science, as an example of such efforts). We anticipate that most if not all TB-SRN participants who are diagnosed with HIV infection during TB-SRN follow-up will enter the linked IeDEA HIV clinics (usually co-located at the site), permitting additional data collection.

7) “I assume that some of the sites are rural and some urban. I hope the study will take this fact, as well as sex and age, into account.”
We confirm that all studies arising from the IeDEA TB-SRN cohort data will consider age and sex as a biological variable. The TB-SRN baseline data collection captures rural/urban residence of the participants and we collect rural/urban location of the study sites through a site characteristics and capacity survey that is distributed to all IeDEA sites every 2-3 years—data collection for the most recent survey is expected to be completed by December 2023. This “Site Assessment” survey data will be available to investigators working with TB-SRN data.

8) “What will happen to the (unfortunately, presumably many) patients who stop TB therapy or stop coming to the clinic? Or, presumably, the coinfected patients who stop their HIV treatment?”
All sites have procedures for tracing and attempting to re-engage patients, including working together with local TB programs to link them back into care and treatment. We are capturing treatment interruption and participant loss-to-follow-up (LTFU) as potential outcomes of TB treatment as well.

9) “Perhaps I missed this, but where are the proposed data-gathering forms? Shouldn’t they be in a supplement? In general, the methodological aspects of the study are not sufficiently specified.”
We have revised our Supplementary Materials to include a PDF containing core data collection forms. However, we are unable to include validated instruments such as the SGRQ, AUDIT, or ASSIST due to licensing requirements and have noted that in the PDF. We have updated the manuscript to refer to these materials.

METHODS AND ANALYSIS, Assessments and data collection: Paragraph 4 (revised):
A copy of the paper CRFs is provided (Supplementary Materials 1).

Specific Comments

10) 9 45-46 “PTLD” is used without having been defined (the first place I see is page 16, line 10).
PTLD is defined in the abstract (page 3) and the introduction (page 5), but we recognize the value of minimizing use of abbreviations and acronyms throughout the text. We have replaced solo usage of PTLD with “post-TB lung disease” throughout the text, while preserving PTLD in parentheses in key places for search engine optimization.

11) 12 14-15 What is “concept driven analysis?”

Within the IeDEA consortium, analyses are developed collaboratively, documented using a “concept sheet” template, and approved by all participating sites and IeDEA regions. Although this is explained in the main text, we recognize there is no space in the Abstract for such detail. To clarify for readers, we have replaced “concept-driven” with “proposed.”

ABSTRACT, Methods and Analysis, final sentence (revised):
Data will be aggregated for proposed analyses.

12) 14 41-45 Are these histories from the patient or from their medical records? Please clarify in the text.
We have added the following sentence to the text to provide clarification on the sources of these data.

METHODS AND ANALYSIS, Assessments and data collection: Paragraph 3 (added):
HIV and TB clinical data will be extracted from medical records and TB registers, while current symptoms, pregnancy history, and history of other conditions will be collected via patient interview.

13) 48-49 Please be specific about the “Specific information” relevant to youth.
We have added examples of data particularly relevant to youth which are captured on the youth demographic form, including orphan status, caregiver characteristics, and school attendance.

METHODS AND ANALYSIS, Assessments and data collection: Paragraph 3 (revised):
Sociodemographic information will be collected including specific information relevant to youth ages 15-24 at enrollment (e.g., orphan status, caregiver characteristics, school attendance).

14) 14/53-15/8 Even assuming that all these instruments are widely validated, it is likely that there are locally applicable cutoffs or interpretations. How do they plan to treat this issue?
We acknowledge the importance of considering local contexts in the interpretation of instrument scores when they have not been re-validated in a given language or population. These points have been discussed with local study sites and considered prior to local IRB review. Whenever available, individual analyses will consider existing evidence for local score cut-offs. This also will be acknowledged as a potential limitation in relevant analyses.

15) 15 30-31 Is this an exhaustive list of all the languages? Have all the translations been tested and validated? If not yet, will they be?
We have expanded this section to specify the languages in which the questionnaires are administered. Translations of a number of the study questionnaires have been previously validated (e.g., PHQ-9, ASSIST). Where this was not already done, regions used culturally adapted versions based on a method previously used by IeDEA.

METHODS AND ANALYSIS, Assessments and data collection, Paragraph 5 (revised):
Research staff will administer questionnaires using relevant local translations (in Bemba, French, Haitian Creole, Khmer, Lingala, Nyanja, Portuguese, Runyankole, Swahili, and Thai) and adaptations as appropriate, implemented in paper CRFs and in the REDCap data collection platform.

16) 16 bottom of table Has LLN been defined? I assume it means “lower limit of normal.” Is “normal” defined by country/site or globally for all sites? Perhaps there is a WHO definition that I (as a statistician not working in this area) am not aware of.
The abbreviation for LLN (“lower limit of normal”) is provided in the text and in the legend of Table 3. We have revised both the text and the table to clarify that this is based on Global Lung Function Initiative (GLI) reference equations.

METHODS AND ANALYSIS, Outcome measures: Paragraph 3 (revised):

Post-treatment outcomes to be ascertained are informed by emerging research surrounding post-TB sequelae.27 40 43 Post-TB lung disease will be defined by new, recurrent or persistent respiratory symptoms or signs that occur post-treatment; hypoxemia (oxygen saturation <90%); pulmonary function impairment; or chest X-ray abnormalities.40 Spirometry definitions for pulmonary function impairment include the following: forced expiratory volume in one second (FEV1) / Forced vital capacity (FVC) ratio < lower limit of normal (LLN), FEV1 <LLN, and/or FVC <LLN. Global Lung Function Initiative (GLI) standard reference equations will be used to calculate LLN (fifth centiles) for each participant; these will be compared with observed values.41 42

17) 19 51-52 or, HIV could modify/moderate the effects of some treatments.
We agree with the Reviewer that this is the case and plan to consider the effect of HIV in our analyses.

18) 54-56 So they expect about 430 “youth with TB” in the study. This seems like a reasonable sample size, and if their description of the current state of knowledge is accurate, something is way better than almost nothing.
We agree with the Reviewer regarding the importance of addressing this knowledge gap.

19) 20 24-25 The “strict protocols…data” should be described.
We have added the following sentence to the section on data management.

METHODS AND ANALYSIS, Data management and harmonization: Paragraph 1 (added):
Study data procedures include methods for ensuring the privacy and confidentiality of participant data, including using codes in place of names, implementing password-protected and encrypted data collection systems, training of site personnel on data management best practices, and applying data pseudonymization where required for compliance with national data protection regulations.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Houben, Rein<br>London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology |
| **REVIEW RETURNED** | 20-Nov-2023 |

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| **GENERAL COMMENTS** | Thanks to the authors for responding to comments from the reviewers. While I may not 100% disagree with all the choices, the choices made are now sufficiently clear for this protocol paper. I look forward to seeing the results from this work. My minor comment is around the subgroups and their analysis, where it would be good to keep track for each patient which subtype of clinical diagnosis was made, and explore this in sensitivity analyses. But no further changes needed to paper in my opinion. |

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| **REVIEWER** | Hertzmark, Ellen<br>Harvard University T H Chan School of Public Health, Global Health |
| **REVIEW RETURNED** | 22-Nov-2023 |

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| **GENERAL COMMENTS** | This version is greatly improved. The only suggestion of mine that has not been addressed is about the timing of subject accession. Is this, perhaps, because the patients/subjects have already been recruited, but the group wishes to publish the protocol before (I hope) doing any analysis? This possibility occurred to me, because they acknowledge the participants (perhaps that is just boilerplate for the final manuscript). |

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| | The attached forms look very detailed, and I hope that the investigators have considered how they want to aggregate the smaller categories (though for a purely descriptive study, this is unnecessary).<br>The large sample size will indeed allow for precise estimates, but it is not clear that these estimates represent anything other than the study group, since they are geographically clumped. Not being an expert, it is conceivable to me that these choices were made because in toto they do represent the world.<br>I wish the authors success. |