THE TB REPRESENTATIVE STUDIES RUBRIC (TB RSR):
A Tool to Enhance Representation in Tuberculosis Clinical Research

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Developed by the Community Research Advisors Group (CRAG), adapting the original Representative Studies Rubric from the Office of HIV/AIDS Network Coordination (HANC) Legacy Project

BACKGROUND AND RATIONALE

Tuberculosis (TB) disproportionately affects many populations that have traditionally been excluded from clinical research, including children, pregnant women, and people living with HIV. Some of the populations most likely to get TB have even been left out of TB clinical trials.[1,2] As a result, new drug regimens for treating and preventing TB are not always accessible to these groups, owing to limited knowledge of safety and efficacy, of appropriate drug doses, and of interactions with other medications. This lack of scientific data makes it difficult to register or recommend new TB treatments in some of the people who need them most, with consequences for both individuals and public health.

The Community Research Advisors Group (CRAG) is the community advisory board to a major international clinical trials network that studies new ways of treating and preventing TB. CRAG members include people who have survived TB, who have cared for people with TB, or who belong to groups at higher risk of the disease and come from communities that host active TB clinical trials. The CRAG has worked together with TB researchers and other community advisors to promote the inclusion of populations affected by TB in research and, where inclusion has been won, has sought to ensure that such inclusion becomes a new norm rather than a special exception.[3]

The TB RSR allows researchers and community advisors to assess the appropriate inclusion of all TB-affected populations in clinical trials in a timely and effective manner. In this sense, the TB RSR is a tool for assessing whether TB treatment trials represent the types of people who get TB. By documenting the representativeness of TB studies, community advisors and researchers can work together to take the necessary steps to ensure that all people in need of safe and effective options for treating and preventing TB can benefit from research and innovation.

Everyone has the human right to enjoy the benefits and applications of scientific progress. This "right to science" is a fundamental human right found in the Universal Declaration of Human Rights and the International Covenant on Economic, Social and Cultural Rights. A central tenet of the right to science is that the ability of people to participate in science is a precondition for accessing the benefits of science (like new drugs or vaccines).[4] When certain populations are excluded from participating in research — whether intentionally or unintentionally — they are also excluded from sharing in the benefits of that research.[5]

We acknowledge that not all groups can be included in all studies or phases of research, but the CRAG believes there should be a clear and stated rationale whenever certain groups are excluded. Additionally, for groups that are included, studies should be designed to produce meaningful data in those populations and have a clear plan to disaggregate and analyze data to allow for dosage adaptation or specific recommendations, if needed. In instances where groups may be included but at small numbers, it is imperative that they are at least represented, and their data reported. To enhance comprehensiveness, research groups should consider collaborating with other studies on inclusions to ensure a more holistic understanding and representation of key demographics and variables within TB trials and to obtain the data necessary for ensuring access to meaningful scientific advances.

THE TB RSR

Acknowledgement of the human right to science motivated the creation of the original RSR by the HANC Legacy Project, which focused on HIV clinical trials.[6] Based on the original RSR, the CRAG has worked to adapt the tool to the particularities of tuberculosis research, adding additional relevant categories and subcategories. The TB RSR is a questionnaire consisting of 17 questions and sub-questions that examines the representation of study populations in terms of:

- Age
- HIV status
- Sex & gender identity
- Pregnancy
- Drug use
- Comorbidities & concomitant medications
- Different clinical subtypes/expressions/manifestations of tuberculous disease
- Race and ethnicity
- Physical, social, and mental ability, and other relevant dimensions of vulnerability with respect to TB
- TB recurrency

The TB RSR can be implemented in a variety of ways depending on a research team's needs. The TB RSR can be used *retrospectively* to appraise representation of study populations within completed or ongoing studies. More proactively, the TB RSR can be implemented *prospectively* during protocol development. When used prospectively, the RSR can ensure that study teams address critical questions pertaining to the enrollment of underrepresented populations, thus serving as a tool to facilitate representativeness, scientific integrity, and the application of scientific progress for those who need it most.[7] Used in this way, the TB RSR helps to flip the usual script: from one where certain population are excluded from studies by default, to one where inclusion is the starting assumption, and the onus is put on researchers to explain why a study cannot or should not enroll certain groups.

The HANC Legacy Project and the CRAG recommend that research teams operationalize the TB RSR early in the development of each study protocol. It can be used as a checklist to clearly define the study population and provide scientific justification for excluding groups, or it can be used to facilitate discussion among study teams who might not otherwise consider the questions of representation that the TB RSR poses. In short: the RSR provides community advisers, funders, and researchers with another tool they can use to leverage clinical trials protocol reviews to unlock the inclusion of key groups in TB research.

THE TUBERCULOSIS RSR QUESTIONNAIRE

Study number and title: _____

Countries of enrollment: _____

Study size (sample size): _____

AGE

1. For phase IIa trials onwards: Are people in the following age categories eligible to participate?
For studies whose eligible population includes one category partially, answer "YES" and then specify the actual eligible age range in "Comments" below:

	Yes	No
0–2	◯	◯
2–5	◯	◯
5–12	◯	◯
12–18	◯	◯
18–34	◯	◯
34–55	◯	◯
55–65	◯	◯
>65	◯	◯

	Yes	No
For age groups that are excluded from participating, does the protocol state a justification for their exclusion?	◯	◯

Comments (include justifications for any exclusions):

PEOPLE LIVING WITH HIV

	Yes	No
2. Are people living with HIV (PLHIV) eligible to participate?	◯	◯
If **yes**, does the protocol limit participation of PLHIV based on CD4 count, viral load, or some other measure and state a justification for this limitation?	◯	◯
If **yes**, does the protocol restrict participation to PLHIV taking certain antiretroviral (ART) regimens and state a justification for this restriction?	◯	◯
If **yes**, does the protocol include analysis of potential drug-drug interactions between TB medicines and antiretrovirals (ARVs)?	◯	◯
If **no**, does the protocol state justification for the exclusion of PLHIV?	◯	◯

Comments (include justifications for any exclusions):

SEX & GENDER INCLUSIVITY

	Yes	No
3. Is the protocol gender-inclusive, meaning cisgender, transgender, and gender nonbinary participants are eligible to participate? Eligible: population is to no extent denied access by the protocol's description of the study population (e.g., answer "No" for protocols that consistently describe the study population in binary terms: men, women, females, boys, girls.)	◯	◯

If **no**, which populations are not eligible?

- ◯ **Cisgender women**
- ◯ **Transgender women**
- ◯ **Transgender men**
- ◯ **Gender non-binary individuals**

	Yes	No
If **no**, does the protocol justify this ineligibility?	◯	◯

SEX & GENDER INCLUSIVITY

	Yes	No
Does intake of medical history questions include the use of gender affirming care?	◯	◯

Comments (include justifications for any exclusions):

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4. For phase IIa trials onwards: Does the protocol include specific plans for disaggregating data and analyzing results by sex and gender?

- ◯ **Yes**
- ◯ **Partially yes — either sex or gender but not both**
- ◯ **No**

If yes, please specify which outcomes will be disaggregated, and by which categories (e.g., sex at birth and gender identity)

Will group outcomes be reported if they do not meet the threshold for statistical analysis, and how?

Comments and justifications:

SEX & GENDER INCLUSIVITY

5. For phase IIa trials onwards & pharmacokinetic (PK) studies: Does the study allow participants to take hormonal treatments (e.g., for menstruation, menopause, contraception, gender-affirming treatment, etc.) and address potential drug-drug interactions between TB medicines and hormonal treatments?

- ◯ **Yes — allowed and addressed**
- ◯ **Yes — allowed but unaddressed**
- ◯ **No — not allowed**

	Yes	No
If hormonal treatments are allowed and specifically mentioned, does the protocol include guidance for adjusting hormone doses in response to known drug-drug interactions?	◯	◯

Comments and justifications, including possible dosage adaptation based upon results:

PREGNANCY

	Yes	No
6. For phase IIb trials onwards or specific PK studies: Is study participation unrestricted for participants who are pregnant? Unrestricted: Participants who are pregnant are allowed to enroll in the study.	◯	◯
If **no**, does the protocol state a justification for restrictions?	◯	◯
If **no**, does the protocol include a plan for handling pregnancies that occur during the trial?	◯	◯
If **no**, are participants who become pregnant during the trial given the option to reconsent and continue participating in the study?	◯	◯
Are pregnant participants living with HIV allowed to enroll in the study?	◯	◯

Comments (include justifications given for any restrictions):

PREGNANCY

	Yes	No
7. For phase IIb trials onwards or specific PK studies: Is study participation unrestricted for participants who are lactating? Unrestricted: Participants who are lactating are allowed to enroll in the study.	◯	◯
If **no**, does the protocol state a justification for restrictions?	◯	◯
If **yes**, does the protocol describe any plan for assessing drug concentrations in breast milk?	◯	◯

Comments (include justifications given for any restrictions):

	Yes	No
8. For phase IIa trials onwards or specific PK studies: Is study participation unrestricted for participants who have the potential to become pregnant? Unrestricted: Participants are fully allowed to become pregnant during the study with no contraceptive requirements.	◯	◯
If **no**, does the study team provide participants with appropriate contraceptive options, including ones that consider cultural values and sensitivities?	◯	◯
If contraception is required, is it oriented only to ciswomen?	◯	◯
If contraception is required, is it justified in the protocol?	◯	◯
If contraception is required, are there exemptions for participants with same-sex partners or those without the ability to become pregnant?	◯	◯

Comments (include justifications given for any restrictions):

PEOPLE WHO USE DRUGS

	Yes	No
9. For phase IIb trials onwards or specific PK studies, especially if regimens tested include a rifamycin class drug: Are people taking opioid substitution therapies (OST) such as methadone eligible to participate? Eligible: Population is to no extent denied access by the protocol's description of the study population. (Answer "No" for protocols that enable the opinion of the investigator to prohibit participation based on past or current drug use.)	◯	◯
If **yes**, does the protocol include analysis of potential drug-drug interactions between TB medicines and OST?	◯	◯
If **yes**, does the protocol include guidance for adjusting OST due to known drug-drug interactions with TB medicines to share with the OST treatment facility and follow up guidance with such facility if needed?	◯	◯
If **no**, does the protocol state a justification for the exclusion of persons who use OST?	◯	◯

Comments (include justifications given for any exclusions):

DIFFERENT EXPRESSIONS OF TB DISEASE

	Yes	No
10. For phase IIa trials onwards: Are people with extrapulmonary TB eligible to participate?	◯	◯
If **no**, does the protocol justify this ineligibility?	◯	◯

Comments (include justifications given for any exclusions):

DIFFERENT EXPRESSIONS OF TB DISEASE

	Yes	No
11. For phase IIa trials onwards: Are there any eligibility restrictions based on severity of TB disease (e.g., extent of cavitation on x-ray).	◯	◯
If **no**, does the protocol justify defining eligibility based on disease severity?	◯	◯

Comments (include justifications given for any exclusions):

OTHER DIMENSIONS OF TB VULNERABILITY

11. For phase IIa onwards: Does the study include language about the participation and data analysis of the following populations?

	Yes	No
People who use drugs, including:		
Alcohol	◯	◯
Tobacco	◯	◯
OST	◯	◯
Other recreational drugs	◯	◯
People with other comorbidities such as:		
People with diabetes	◯	◯
People with hepatitis B	◯	◯
People with hepatitis C	◯	◯
People with cardiopathies/cardiac diseases treated with medications that may interact with TB drugs or for where TB drugs may affect the cardiopathy (e.g., arrythmia vs. medication that prolongs QT).	◯	◯
People with disabilities	◯	◯
Migrant population regardless their residential status	◯	◯
Incarcerated people	◯	◯
If **yes**, is there a specific plan to adapt the informed consent process and privacy protections to the prison setting?	◯	◯

OTHER DIMENSIONS OF TB VULNERABILITY

	Yes	No
13. Does the protocol include specific plans for disaggregating data or analyzing results by race and/or ethnicity?	◯	◯

If **yes**, please list the race and ethnicity categories named in the protocol.

	Yes	No
14. Does the study protocol set specific, measurable enrollment goals or targets for any specific populations (e.g., PLHIV must make-up 20% of the overall study population)?	◯	◯

If **yes**, name the populations and include the corresponding enrollment goals.

	Yes	No
15. Does the study protocol cap the enrollment of any specific population to a certain maximum threshold (e.g., PLHIV cannot make-up more than 20% of the overall study population)?	◯	◯

If **yes**, name the populations and include the corresponding enrollment caps.

If **yes**, is the enrollment cap justified in the protocol?	◯	◯

OTHER DIMENSIONS OF TB VULNERABILITY

16. Do study documents correctly apply best practices to define the study population in terms of:

Gender identity:

- ◯ **Correctly applied**
- ◯ **Incorrectly applied/Not applied**

Sex assigned at birth:

- ◯ **Correctly applied**
- ◯ **Incorrectly applied/Not applied**

Comments (include examples of any discordant language):

17. Do study documents correctly apply the Stop TB Partnership's *Words Matter Language Guide*?

- ◯ **Yes (there is NO stigmatizing language)**
- ◯ **No (there IS stigmatizing language)**

Comments (include examples of any discordant language):

CRAG TB Community Research Advisors Group

hanc HIV/AIDS Network Coordination