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The Representative Studies Rubric:
A Tool to Enhance the Representativeness of Study Populations in Clinical Research

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Background/Rationale

Clinical research, including studies responding to the HIV/AIDS epidemic and other diseases, consistently fails to enroll representative study populations. Cisgender women, transgender people, pregnant people, people who inject drugs, and communities of color in the US—particularly Black, Indigenous, and Latina/e/o/x communities—remain underrepresented. A review of Phase 3 trials for new antiretrovirals (ARVs) found that cisgender White men account for 6% of the global HIV epidemic, yet they represent 51% of participants in randomized controlled trials for new ARVs. This review provides just one example of the ongoing, institutionalized problem of misrepresentation that cuts across all clinical research—therapeutic and preventive, historical and contemporary.

Researchers often mischaracterize underrepresented populations as "hard-to-reach" and "mistrustful." In reality, the underrepresentation of these populations stems from a legacy of patriarchal, colonial, and racist policies and practices that have been institutionalized within the field of research. For example, most researchers have only recently begun to collect transgender-inclusive data from study participants. The erasure of transgender people from data represents policy and practice that mars transgender representation in clinical research—not a failure of transgender people to participate in research.

The International Covenant on Economic, Social, and Cultural Rights, signed but not ratified by the United States, defines "the right of everyone to enjoy the benefits of scientific progress and its applications." While cisgender White men reap the benefits of clinical research—in which they are vastly overrepresented—underrepresented populations suffer the serious consequences of their exclusion. For example:

- Due to the DISCOVER study's exclusion of people assigned female at birth, the United States FDA could not approve Descovy for PrEP in this population, thus exacerbating existing gaps in PrEP coverage.
- On average, people who can become pregnant have to wait six years after licensure of ARVs before any published data are available demonstrating safety and efficacy of the same ARVs in pregnancy.
- Black, Indigenous, and Latina/e/o/x Americans continue to be underrepresented in HIV clinical research, while HIV-related disparities for these populations continue to grow.

Since 2009, the HANC Legacy Project has worked nationally to increase awareness of and build support for HIV clinical research by addressing factors that influence the participation of historically underrepresented communities. Over the years, The Legacy Project has worked collaboratively with Community Partners, the NIAID Division of AIDS Cross-Network Transgender Working Group, the HIV Prevention Trials Network Black Caucus, the Women's HIV Research Collaborative, and many additional partners to produce numerous trainings,

guidance documents, statements, and calls to action to enhance the representativeness of study populations in HIV/AIDS clinical research. While many of these interventions have been implemented to some extent, they have not been fully optimized, and HIV clinical research continues to exclude and under-enroll the aforementioned populations.

The Representative Studies Rubric (RSR)

Building on the existing work of the HANC Legacy Project, we have designed a tool, the Representative Studies Rubric (RSR), to guide and monitor enhanced representation in clinical research. The RSR assesses individual studies for the extent to which they are designed to include or exclude underrepresented populations. The RSR consists of a twelve-item questionnaire that examines the representation of study populations in terms of:

- age
- ethnicity
- gender
- injection drug use
- pregnancy
- race, and
- sex assigned at birth.

The RSR is also designed to identify erroneous and inappropriate language used in protocols, as language itself can exclude or otherwise impede the participation of underrepresented populations.

The RSR can be implemented in a variety of ways depending on a research team's needs. For example, the RSR can be used retrospectively to appraise representation of study populations within a research team's portfolio of studies that have already made it into the field. More importantly, the RSR can be implemented *proactively* during protocol development. When used proactively, it can ensure that study teams address critical questions pertaining to the enrollment of underrepresented populations, serving as a tool to facilitate inclusion, scientific integrity, and the application of scientific progress for those who need it most.

The HANC Legacy Project recommends that research teams operationalize the RSR early in the development of each study protocol. It can be used simply as a checklist to clearly define the study population and provide scientific justification for the exclusion of any underrepresented group(s). It can also be used to facilitate scientific discussion among study teams who might not otherwise consider the questions of representation that the RSR poses. Two of the items in the RSR also include hyperlinks to guidance documents by which individual studies can be measured for inclusion and accurate language. When meaningfully implemented, the RSR can help to create a future for science that honors *everyone's* right to enjoy the benefits of scientific progress and its applications.

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The RSR Questionnaire (in raw format; format to be adapted based on need)

Study number and title:
Countries of enrollment:
Study size:

1. **Are people in the following age categories eligible to participate?**
   (For studies whose eligible population extends only partially into a category listed below, e.g. 0-10 instead of 0-12, answer "Yes," and then specify the actual eligible age range in Comments below.)
   a. 0-12 [Yes] [No]
   b. 12-18 [Yes] [No]
   c. 18-34 [Yes] [No]
   d. 34-55 [Yes] [No]
   e. ≥55 [Yes] [No]

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

   Comments:

2. **Are cisgender women eligible to participate?** (Cisgender women are people assigned female at birth who identify as women.)
   Eligible: Population is to no extent denied access by the protocol's description of the study population.
   a. Yes
   b. No
      i. Does the protocol state justification for the exclusion of cisgender women?
         1. Yes
         2. No

   Comments:

3. **Are gender nonbinary individuals eligible to participate?** ("Gender nonbinary" is an umbrella term used to describe people who do not identify their gender solely as 'man' or 'woman,' regardless of the sex they were assigned at birth.)
   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, males, females, boys, girls*.)
   a. Yes
   b. No

i. Does the protocol state justification for the exclusion of gender nonbinary individuals?
    1. Yes
    2. No

Comments:

4. **Are persons who inject drugs 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 enable the opinion of the investigator to prohibit participation based on drug use.)
    a. Yes
    b. No
        i. Does the protocol state justification for the exclusion of persons who inject drugs?
            1. Yes
            2. No

Comments:

5. **Are transgender men eligible to participate?** (Transgender men are people assigned female at birth who identify as men.)
   Eligible: Population is to no extent denied access by the protocol's description of the study population.
   (E.g. Answer "No" for studies that refer to the study population as "women.")
    a. Yes
    b. No
        i. Does the protocol state justification for the exclusion of transgender men?
            1. Yes
            2. No

   Comments:

6. **Are transgender women eligible to participate?** (Transgender women are people assigned male at birth who identify as women.)
   Eligible: Population is to no extent denied access by the protocol's description of the study population.
   (E.g. Answer "No" for studies that refer to the study population as "men," "MSM," or other terms that deny access to transgender women.)
    a. Yes
    b. No

i. Does the protocol state justification for the exclusion of transgender women?
    1. Yes
    2. No

Comments:

7. Is study participation unrestricted for participants with pregnancy potential?
Unrestricted: Participants are allowed to be pregnant or become pregnant during the study with no contraceptive requirements.

a. Yes
b. N/A (not enrolling any participants with pregnancy potential)
c. No
    i. Does the protocol state justification for restrictions?
        1. Yes
        2. No

Comments:

8. Does the study include specific and measurable goals/plans to enroll:

a. American Indians / Alaska Natives [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
b. Black Americans [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
c. Cisgender women [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
d. Latina/e/o/x people in the US & territories [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
e. People in specific age groups [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
f. People who inject drugs [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]
g. Transgender people [Yes, enrolling with goals/plans] [No, enrolling without goals/plans] [Not enrolling this population]

Comments (state what the enrollment goals are (if any) and what resources are available to achieve them):

9. Does the community engagement strategy prioritize underrepresented populations relevant to the study?

a. Yes-Specific
b. Yes-General
c. No

Comments:

10. **Does the protocol include sex-specific and/or gender-specific statistical plans (e.g. menstruation, menopause, biological tissues, endogenous/exogenous hormones, etc)?** (Answer Yes-Specific for studies exclusively enrolling a single sex/gender group.)

    a. Yes-Specific
    b. Yes-Vague
    c. No

    Comments:

11. **Do study documents correctly apply the DAIDS Cross-Network Transgender Working Group guidance to define the study population in terms of:**
    a. Gender identity [Correctly applied] [Incorrectly applied / Not applied]
    b. Sex assigned at birth [Correctly applied] [Incorrectly applied / Not applied]

Comments:

12. **Do study documents correctly apply the NIAID HIV Language Guide?**
    a. Yes (there is NO stigmatizing language)
    b. No (there IS stigmatizing language)

Comments: