Division of AIDS Cross-Network Transgender Working Group

Guidance on the Use of Gender-Inclusive HIV Research Practices:

Protocol Design, Data Collection, and Data Reporting

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Background and Purpose

The Division of AIDS (DAIDS) Cross-Network Transgender Working Group (CNTWG) was established in December 2014 to foster coordination, collaboration, and an exchange of information related to transgender issues across the NIH-funded HIV/AIDS clinical trials networks. The primary goal of this working group is to create an HIV research environment that promotes transgender inclusion, especially of transgender people in racial and ethnic minority communities given the high burden of HIV in those communities. Toward that end, in April 2015, the working group recommended the consistent use of the two-step method for collecting data on gender identity and sex assigned at birth across the networks and has developed a comprehensive transgender training curriculum for network and site staff. The Transgender Training Curriculum for HIV Research developed by the CNTWG includes five training modules, three of which are available as e-learning and in-person training tools on the DAIDS Learning Portal (https://daidslearningportal.niaid.nih.gov/) and two of which are forthcoming. Numerous training sessions utilizing the curriculum have been conducted at network meetings.

To supplement the trainings, the CNTWG believes additional guidance would be valuable in helping the NIH-funded HIV/AIDS clinical trials networks implement gender-inclusive practices.

This guidance document highlights a number of different practices that can facilitate gender-inclusiveness in study protocol design, data collection, and data reporting across the networks, and provides needed context and direction to support these efforts.

The purpose of this guidance is to:

1. Reiterate that all studies should be gender inclusive, allowing for the enrollment of transgender[1] as well as cisgender participants unless there is a scientific reason to limit enrollment, with the rationale for exclusion provided in relevant study documents.
2. Reinforce the importance of collecting data on study participants' gender identity and sex assigned at birth using the two-step method.
3. Ensure that the NIH-funded HIV/AIDS clinical trials networks accurately and appropriately describe the study population in terms of gender identity and sex assigned at birth in all research protocols in a systematic way. This includes the use of non-stigmatizing, gender-inclusive language in research protocols and data reporting.

[1] The term transgender is being used as an umbrella term that includes transgender men, transgender women, gender non-binary and gender non-conforming individuals, and all people whose gender identity does not match their sex assigned at birth. In places, this guidance refers more specifically to transgender women and transgender men. A transgender woman is someone who identifies as a woman but was assigned male at birth, and a transgender man is someone who identifies as a man but was assigned female at birth.

4. Encourage the accurate description of the study population in terms of gender identity and sex assigned at birth when enrollment and other study data are published and/or presented.

Rationale

These standard practices are intended to guide protocol teams and network staff in protocol design, data collection, and data reporting. The use of accurate language as it relates to gender identity and sex assigned at birth will yield better data, support the generalizability of study findings by including a more diverse participant population, help build rapport between researchers and participants, and facilitate transgender outreach/recruitment and retention. Neither transgender individuals nor any potential study participants should be expected to determine their own eligibility for research studies as a result of imprecise language related to gender identity and sex assigned at birth.

Additionally, improving data reporting practices with regard to gender increases the research team's ability to report results in a manner that is scientifically accurate and relevant to the communities in which we work. To date, data on transgender populations are limited and often combined with data on cisgender individuals. It is not only important that transgender people feel "counted" when they participate in our research studies, but comprehensive data reporting on enrollment is essential to help identify research gaps, determine if the results are generalizable to transgender people, and increase our understanding of why transgender people may or may not be participating in biomedical HIV research funded by DAIDS. This is critical given the disproportionate impact of HIV in transgender communities, particularly communities of color.

Finally, capturing data on gender and sex assigned at birth, in addition to data on sexual orientation, race and ethnicity, would also facilitate data reporting and potentially analyses that include the intersection of these demographic characteristics. Data yielding intersectional analyses offer more nuanced and potentially more useful information than data that are limited to single-variable analysis. For example, data that reflect participants as whole people (e.g. non-Hispanic Black cisgender heterosexual women) may allow for more real-world interpretations and applications than data analyzing only one participant characteristic at a time (e.g. cisgender women). Participant data should therefore be reported and analyzed with these intersections in mind where possible.

Use of Accurate Language in Protocols

1. **Protocol/Study Title – If the title of the protocol or study identifies a specific study population, it should describe the study population using the terms *cisgender* and *transgender*.** For example, a phase 2 injectable PrEP study that limits enrollment to participants who were assigned male at birth and identify as men should be titled, "A Phase 2 Study of Injectable PrEP in **Cisgender Men**." It harms trust in the research and compromises recruitment to use the general terms "women" and "men" if a study is not open to all potential participants who identify as women or men. On the other hand, if a study does not seek to recruit a specific population, the terms "individuals" or "adults" are appropriate to indicate that people of all gender identities, including gender non-binary individuals, are included.

   Specificity in the protocol title, when appropriate, can help avoid confusion and discouragement for potential study participants, as exemplified in the following scenario: A transgender man scheduled an appointment to enroll in one of the NIH-funded HIV/AIDS clinical trials network's research studies that was titled for "men." When he arrived, he learned that the study was only enrolling individuals assigned male sex at birth, and that he was not eligible to participate. He left feeling humiliated, angry,

frustrated, and disappointed that he was unable to participate because the study was limited to cisgender men. After that experience, he is unlikely to seek information about future studies, unless he can be certain he is considered part of the study population.

2. **Protocol overview/background – When the study population is described for the first time, it should be clearly defined.** To define the study population, the following terms may be used, depending on the study:
    - Cisgender
    - Transgender
    - Gender non-binary
    - All individuals

    Acronyms and abbreviations may be identified for subsequent references to the study population (e.g. transgender woman [TGW], transgender man [TGM], etc.).

    If required, participants' sexual practices should also be described (e.g. individuals who have receptive anal and/or vaginal sex with cisgender men). While the term "men who have sex with men" (MSM) is commonly used, it is important to clearly state whether the term "men" includes transgender men as well as cisgender men.

3. **Rationale for selection of study population –** The NIH Revitalization Act of 1993 (the Act) requires that women and minority groups be included in all NIH-funded clinical research, unless a clear and compelling rationale establishes that inclusion is inappropriate.[2] The Act also requires that the composition of the study population is addressed in terms of "sex/gender and racial/ethnic group" in study proposals. [Note: the authors of this guidance interpret the language in the Act to mean that the *study population should be described in terms of sex, gender, race, and ethnicity, since sex and gender are not the same, and race and ethnicity are not the same.*]

    In accordance with the NIH Revitalization Act, the study population section of all study protocols should describe potential participants in terms of gender identity and sex assigned at birth. When cisgender women and minority groups (including transgender people, whom the NIH has formally designated a "health disparity population" along with other sexual and gender minorities[3,4]) are excluded from a study, this section of the protocol should clearly explain why their exclusion is necessary. The Act applies to all Phase III and "pivotal Phase II and IV" studies, but the authors of this guidance recommend that *all* clinical research conducted by the NIH-funded HIV/AIDS clinical trials networks includes cisgender women and minority groups, including transgender people, "unless a clear and compelling rationale establishes that inclusion is inappropriate."

    The designation of sexual and gender minorities as a "health disparity population" acknowledges the unique health challenges faced by these communities and the need for focused research that would help minimize the disproportionate impact of various diseases and conditions. This is highly relevant for the NIH-funded HIV/AIDS clinical trials networks. By capturing data and accurately reporting on the

[2] https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm
[3] https://www.niaid.nih.gov/grants-contracts/sex-gender-minorities-health-disparity-population
[4] https://www.nimhd.nih.gov/about/directors-corner/messages/message_10-06-16.html

number of transgender people in our studies, we can begin to address the disproportionate impact of HIV on transgender communities.

4. **<u>Eligibility criteria</u> – This section of the protocol should specify sex assigned at birth, gender identity, and gender-related factors, among other criteria required for eligibility.** These include:
    - The sex assigned at birth of participants who are eligible for the study (i.e. *assigned female sex at birth*, *assigned male sex at birth*, *assigned any sex at birth*).
    - The gender identity of participants who are eligible for the study (e.g. *people of all gender identities*, *cisgender women*, *transgender men*, etc.).
    - Other eligibility factors for inclusion/exclusion (e.g. gluteal implants or fillers, hormone use, HIV status, prior ART use, childbearing potential, etc.).

    When addressing childbearing potential, terms such as "individual of childbearing potential" or "people of childbearing potential" are preferred instead of "women of childbearing potential" or "females of reproductive potential," since transgender men and people assigned female at birth who identify as gender non-binary may also be of childbearing potential. Similarly, the term "men/males of reproductive potential" is not fully accurate as people assigned male at birth who do not identify as men may be of reproductive potential as well. Also, since people who do not identify as women or mothers can become pregnant and give birth, the term "perinatal transmission" should be used instead of "mother to child transmission". "Mother-to-child" transmission is also problematic because it is stigmatizing. (A list of selected non-stigmatizing terms can be found in Appendix A.)

    Laboratory values are another area of concern. Certain laboratory values may be included in eligibility criteria, such as hemoglobin, creatinine, and some hepatic markers, among others. Gender-affirming hormone therapy, however, can shift the "lab normal" ranges, making potential transgender participants ineligible by virtue of having their lab values evaluated according to their sex assigned at birth rather than by their gender identity.

    One example of laboratory inclusive values is being used in the Antibody Mediated Prevention Study (HVTN 704/HPTN 085): Hemoglobin (Hgb) ≥ 10.5 g/dL for volunteers who were assigned female at birth, ≥ 13.0 g/dL for volunteers who were assigned male at birth (≥ 12.0 g/dL for transgender women taking feminizing hormones [e.g., anti-androgens, estrogens]).

    For each study, the protocol team should carefully consider how eligibility lab values are stated and whether they can be differentiated by factors such as gender identity, sex assigned at birth, and hormone use to facilitate the inclusion of transgender participants.

    Even after enrollment is complete, clinical trials may be in a unique position to contribute to the limited information on true "lab normal" ranges in persons taking exogenous, gender-affirming hormone therapy when reporting study data.

5. **<u>Demographic data collection</u> – As per the recommendation from the DAIDS Cross-Network Transgender Working Group and generally accepted best practices,[5] the NIH-funded HIV/AIDS clinical**

[5] UCSF Center of Excellence for Transgender Health, https://prevention.ucsf.edu/transhealth/education/data-recs-long; The Institute of Medicine, https://www.ncbi.nlm.nih.gov/pubmed/22013611; World Professional Association for Transgender Health (WPATH), https://wpath.org/media/cms/Documents/SOC%20v7/Standards%20of%20Care_V7%20Full%20Book_English.pdf; \; Fenway Institute National LGBT Health Education Center, https://fenwayhealth.org/new-paper-offers-recommendations-for-collecting-so-gi-patient-data/

trials networks should always collect data on study participants' gender identity and sex assigned at birth using the two-step method, unless there is concern of undue discrimination, stigma, and/or harm. (See Appendix B for a description of the two-step method) Accurate collection of gender identity avoids incorrectly categorizing transgender individuals as cisgender men or cisgender women; prevents marginalization of transgender people; and advances scientific knowledge about the impact of hormone therapy, gender-affirming body modifications, and social/structural factors on HIV cure, treatment, and/or prevention interventions.

Furthermore, while gender identity is typically collected only at baseline, it may be valuable to gather information on gender identity using the two-step method at the time of enrollment AND at later points in the trial. During the conduct of HVTN 505, for example, approximately 10-15 percent of all transgender participants did not initially identify as transgender but for a variety of reasons did so later in the trial. **Given that gender identity is often fluid, and that participants may not be comfortable disclosing their identity to a staff member with whom they do not yet have a trusting relationship, the protocol team should make an informed decision based on the objectives and population for that specific study, and should carefully consider whether to collect gender identity data at timepoints beyond baseline.**

Accuracy of Language in Data Reporting and Analyses

The NIH Revitalization Act of 1993 strongly encourages sex differences to be reported in results for all NIH-funded clinical research study publications. **Given that the NIH-funded HIV/AIDS clinical trials networks now collect data on gender identity and sex assigned at birth, it is important to report differences associated with gender identity and sex assigned at birth in study results when the data are published and presented. Reporting these results begins with reporting the number of transgender participants enrolled in a study—even if that number is zero.** If there are too few transgender participants to support specific analyses, that can be noted as a limitation when the results are reported. Acknowledging the number of transgender individuals in studies will help identify gaps in study participation, and possible study outcomes and the reasons for them.

In a recent Lancet HIV article "Transgender HIV research: nothing about us without us,"[6] the authors reflected on the lack of inclusion of transgender scientists and researchers at the 2019 International AIDS Society (IAS) conference and took issue with the way in which data were reported. While they were making specific recommendations for IAS, they make important points that are relevant to NIH-funded clinical HIV research. For example, they noted the following:

> *"Responding to calls for disaggregation of transgender women in studies of men who have sex with men, abstract titles increasingly refer to men who have sex with men and transgender women. Such inclusion is often only nominal; at the 2019 IAS meeting, 51 abstracts mentioned transgender people in the title. Of these, only 34 disaggregated data for transgender participants from cisgender participants or were exclusively about transgender people. Further, transgender status does not constitute a behavioural risk for HIV. Trans people can be lesbian, gay, bisexual, queer, asexual, or heterosexual; a substantial number of trans women are at little risk of HIV because they are sexually inactive or sexually active with cisgender women, whereas a large number of trans men are at risk of HIV, because they are sexually active with cisgender men. Yet, only six abstracts at IAS 2019 specified the risk group to which transgender study participants belonged."*

[6] https://doi.org/10.1016/S2352-3018(19)30269-3

This article underscores the importance of not only collecting data on participants' gender identity, but the need to report on it accurately as well. This is critical to understanding the impact of HIV prevention and treatment interventions. Clearly, results from studies enrolling only cisgender men are not generalizable to cisgender women, and vice versa. One specific example is the IPERGAY study,[7] which found that intermittent dosing of oral Truvada® as PrEP provided protection from HIV acquisition among cisgender men who have sex with men. These results do not apply to cisgender women because this population was not enrolled in the IPERGAY study. In fact, separate analyses[8] suggest that intermittent dosing of oral PrEP does *not* provide the same level of protection from HIV acquisition among cisgender women. More recently, following the DISCOVER trial conducted by Gilead to assess whether F/TAF (Descovy) was as safe and effective as F/TDF (Truvada®) when used as daily oral PrEP, the US Food and Drug Administration (FDA) could only approve the drug for use as PrEP in cisgender men and transgender women who have sex with cisgender men; the approval specifically excludes individuals vulnerable to HIV through receptive vaginal sex because such individuals were not included in the study. These examples from oral PrEP research illustrate that results from studies enrolling only cisgender people may not be generalizable to transgender people. Therefore, study results should clearly describe the study population using the terms *cisgender*, *transgender*, and *sex assigned at birth,* so it is clear to whom the study results apply.

Summary

The DAIDS Cross-Network Transgender Working Group recommends that the NIH-funded HIV clinical trials networks adopt these guidelines in order to more effectively recruit and enroll transgender individuals, more accurately report scientific results, and increase our understanding of transgender communities in the context of HIV treatment, prevention, and cure research.

[7] https://www.nejm.org/doi/full/10.1056/nejmoa1506273

[8] http://www.aidsmap.com/news/sep-2017/experts-concur-event-related-oral-prep-probably-wont-work-women

Appendix A

Use of Non-Stigmatizing, Gender-Inclusive Language

Instead of….	Use….	Why….
Biological sex	Sex assigned at birth	Transgender people are biological beings, and this terminology discounts that
Sex at birth	Sex assigned at birth	Sex is assigned, not a given; many transgender and intersex individuals feel they were "assigned" the wrong sex at birth
A transgender	Transgender person, a person who is transgender	Transgender is properly used as an adjective; it's use as a noun is offensive
Transgenders	Transgender people, people who are transgender	The word "Transgender" cannot be made plural
Transgendered	Transgender	This is stigmatizing language, presuming that gender is something that happened in the past tense
Used to be a woman, born a woman, FTM	Transgender man, trans man	This is stigmatizing language that emphasizes the past without acknowledging the present
Used to be a man, born a man, MTF	Transgender woman, trans woman	This is stigmatizing language that emphasizes the past without acknowledging the present
Transgendering, sex change, pre-operative, post-operative, The surgery	Gender affirmation, transition, or transitioning	Gender affirmation and transition reflect the process someone goes through to receive personal and/or social recognition and support for their gender identity and expression. This process can have social, legal, psychological and sometimes medical components.

Appendix A (continued)

Use of Non-Stigmatizing, Gender-Inclusive Language

Instead of….	Use….	Why….
Hermaphrodite	Intersex person, person who is intersex	Intersex is a term used for a variety of conditions in which a person is born with reproductive and/or sexual anatomy that doesn't seem to fit the typical definitions of female or male. The Intersex Society of North America recommended against using the term *hermaphrodite* since it fails to reflect modern scientific understandings of intersex conditions and is both misleading and stigmatizing.
Sexual preference	Sexual orientation	"Preference" suggests that non-heterosexuality is a choice
Women of childbearing potential	Individuals or people of childbearing potential	People of all genders may have childbearing potential
Men with reproductive potential	People with reproductive potential	People of all genders may have reproductive potential
[Women or men] who have sex with men	[Cisgender women, cisgender men, transgender women, transgender men, transgender people or more broadly, individuals] who have sex with [cisgender or transgender men]	Using "men and women" as a proxy for "everyone" excludes people who identify as transgender, non-binary, and other gender identities. It is also necessary to specify the gender identity of sexual partners.
Men or women over X years of age	Individuals over X years of age	Using "men and women" as a proxy for "everyone" excludes people who identify as transgender, non-binary, and other gender identities
Men and women	Individuals or people of all genders, or be specific – cisgender men and cisgender women	Using "men and women" as a proxy for "everyone" excludes people who identify as transgender, non-binary, and other gender identities

Appendix B

Data Collection: The Two-Step Method

The two-step method for collecting data on participants' gender identity and sex assigned at birth is considered a best practice and is recommended by all leading transgender organizations as well as the Institute of Medicine. Step one of this method asks about participants' current gender identity and includes a variety of options to choose from. Step two asks about the sex they were assigned at birth.

This method allows us to accurately identify and categorize study participants. The likelihood of mis-categorizing transgender study participants is high if this method is not used (e.g. a participant who checks "Woman" as her gender identity may have been assigned male at birth, and a participant who checks "Female" sex assigned at birth may identify as a man, gender non-conforming, or any other gender identity). Collecting accurate demographic data is crucial to understanding how study interventions may (or may not) work differently across populations.

1. What is your current gender identity?

- ☐ Cisgender Man
- ☐ Cisgender Woman
- ☐ Genderqueer
- ☐ Gender Non-binary
- ☐ Gender Non-conforming
- ☐ Man
- ☐ Transgender Man/Trans Man
- ☐ Transgender Woman/Trans Woman
- ☐ Two-Spirit
- ☐ Woman
- ☐ Additional Category, Please Specify_____
- ☐ Decline to Answer

2. What was your sex assigned at birth?

- ☐ Female
- ☐ Male
- ☐ Intersex
- ☐ Decline to answer

In this example, options are listed alphabetically to avoid the perception of hierarchy. People are given the opportunity to specify their gender identity using a term not listed on the form (the category of "Other" is avoided as it is not anyone's identity), and they may also decline to answer. Intersex has also been included as an option for sex assigned at birth because official documents recognizing intersex status are becoming more available to intersex people (even in cases where the sex initially assigned at birth was not intersex). Because the question about sex assigned at birth can be problematic for some transgender and gender non-conforming people, it is best to include a "decline to answer" option and also a rationale for asking this question, such as, "some biological processes are impacted by the sex you were assigned at birth, so it is important to record this information." The rationale can easily be included with instructions given to staff who are administering the collection of demographic data, or it can be included next to the question if being asked in a survey/questionnaire format.