GENDER EQUALITY TOOLBOX

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PROGRAM OFFICER JOB AID

Questions to Assess Grantee's Plans to Address Sex and Gender in Clinical Trials

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This job aid was prepared for the Global Health Discovery and Translational Sciences team and the Gender Equality team of the Bill & Melinda Gates Foundation by Julie Becker, Executive Vice President, and Saroj Sedalia, Vice President, at Rabin Martin. Valuable technical review and inputs were provided by Sandra Laney, Rebekah Neal, Jessica Jones, Jennifer McCleary-Sills, Peter Dull and Graham Snead (the Bill & Melinda Gates Foundation).

BACKGROUND

This document is intended to support Bill & Melinda Gates Foundation program officers in helping grantees to implement gender-intentional trials as part of the foundation's commitment to addressing gender equality across its work. The research was conducted in response to a question of how gender is used in clinical trials. The Global Health strategies at the foundation engage partners running clinical trials to varying degrees and there wasn't a direct or consistent answer to the question, so the foundation partnered with Rabin Martin to determine how and when gender is currently factored into clinical trials and identify opportunities to run a more intentional trial.

In gender-intentional trials, researchers consider how gender inequalities affect trial processes and outcomes, ensure they do not exacerbate existing inequalities, and consider sex as a biological variable.

A gender-integrated clinical trial is a clinical trial that:

- Has appropriate[1] sex representation in the study population;
- Considers and seeks to address underlying gender norms and inequalities in clinical trial practices;
- Conducts sex-disaggregated analysis, and disseminates results of sex-disaggregated analyses and any gender-related data publicly.

Gender inequalities—and the social norms, roles and relationships of and between women and men—can affect trial outcomes by presenting barriers to effective recruitment, retention and adherence. Gender can also influence ethical conduct of trials and good public health and development practices that should be used in clinical research for public health products supported by the foundation. Gender issues are of particular concern in contexts where persistent gender inequalities and women's limited autonomy affect their ability to consent and participate, or to support the participation of their children in clinical trials.

Sex is also an important factor in clinical trials. When clinical trials of biomedical products lack appropriate[2] numbers of male and female participants to detect trends or differences in effect, or when they fail to conduct sex-disaggregated analysis, the results may be representative of only half the population, and differences in effect may be overlooked. Further, failure to disseminate these analyses limits the broader global health and research community's ability to learn from the findings of others.

Sex	Gender
Refers to the biological differences among sexes	Refers to the economic, social and cultural attributes and opportunities associated with being a particular sex in a particular social setting at a particular point in time
Physiological differences among sexes	Socially determined characteristics assigned to particular sexes
e.g. Male vs. female	e.g. Masculine vs. feminine
Same across all parts of the world and across different times	Culturally and socially determined, therefore variable

JOB AID OVERVIEW

This job aid[3] should be used as a complement to the foundation's Grantee Guidance on Gender Considerations in Clinical Trials, which serves as a reference for developing gender intentional clinical trials. It is designed to be used when reviewing proposals, and as a reference throughout the course of the trial while reviewing reports, making site visits or participating in meetings with the grantee.

The content is organized around clinical trial processes, including: study design and site selection; recruitment, enrollment, retention and adherence; social impact of participation; analysis; and community engagement. Each section includes a set of questions that prospective grantees should answer within their requests for funding. These questions also appear in the grantee guidance document in a consolidated form. The grantee guidance document can be used both as a resource for proposal development and as a reference for grantees currently implementing clinical trials.

This job aid is also intended to complement the Good Participatory Practice Guidance (GPP), which does not currently address gender issues explicitly. GPP focuses specifically on HIV and TB trials, but provides broader and more in-depth guidance on many of the issues covered in this job aid and the Grantee Guidance, with a focus on stakeholder and community engagement.

COMMUNITY ENGAGEMENT

Questions for grantees

1. How will you ensure both women and men meaningfully participate in community engagement activities throughout the trial process (e.g. community advisory boards)?

What to look for in grantee responses on community engagement (examples):

Is there a community engagement plan that specifically addresses gender representation, gender-power dynamics and attention to gender concerns? See the GPP for more ideas and considerations.

PRE-TRIAL (STUDY DESIGN + SITE SELECTION)

Questions for grantees

1. Will your trial enroll men and women?

- If no, please provide your rationale and/or evidence to support the exclusion of either men or women.
- If yes, please indicate your targeted composition of the proposed study population and provide an evidence-based rationale for this composition. Please include any evidence from prior studies indicating whether sex differences in effect of the product are expected.
- If yes, and this is a phase III trial, will your study be powered to test differences in effect by sex or is it designed to detect trends? Please provide a rationale to support your response.

2. What gender considerations will you take into account in site selection and preparatory research?

3. How does the study design inform future product introduction and uptake for women and girls (where relevant), or take gender into account in cases where women play a key role in product uptake (e.g. child immunizations)?

What to look for in grantee responses on trial design (examples):

- Is there sound rationale for excluding men or women from the trial (in cases where one or the other has been excluded)?
- In cases where recruitment goals are not sex-balanced, is there evidence justifying the imbalance? For example, are they proposing enrolment proportional to disease burden? Will they be able to detect trends in effect when disaggregating the data by sex?
- Have they shown sufficient evidence from pre-clinical research or early clinical research to suggest whether sex differences are a concern, and have they designed the trial appropriately to detect any potential differences or trends?
- Does the grantee indicate sufficient knowledge of local gender roles and gender-related barriers? If not, have they included activities to gather information or improve their knowledge?
- Have they considered the role of gender in eventual product introduction and use? For example, is gender considered in the target product profile? Have they considered gender differences in acceptability of routes of administration?

RECRUITMENT, ENROLLMENT, RETENTION AND ADHERENCE

Questions for grantees

1. What difficulties do you anticipate in recruiting males or females? What strategies will you use to recruit and retain men and women (or boys/girls) that take potential gender barriers into account?

2. In contexts where women have limited autonomy and lower literacy levels than men, how will you ensure that informed consent processes meet women's needs[4] and achieve fully informed and voluntary consent?

3. How will you address the potential influence of gender on adherence (if applicable) to study products, contraceptive requirements or other trial procedures/requirements?

4. Will the trial include other key populations that may have different levels of autonomy or power, such as transgender or MSM populations? What concerns might you expect related to their recruitment, enrollment, retention and adherence, and how will you address them?

What to look for in grantee responses on recruitment, enrollment, retention and adherence (examples):

Recruitment:

- Have they proposed gender-specific recruitment strategies that consider knowledge of local gender roles and gender-related barriers to participation (e.g. whether men in the community migrate for work, whether women have mobility restrictions; whether pregnancy testing presents a cultural barrier)?

- If the trial is recruiting children, have they considered potential parental gender preference in enrollment (e.g. reviewed literature on or cited knowledge of gender preference in context, planned to monitor sex balance in trial population, included in formative research)?

- If little or no information is available on gender-related barriers to recruiting and retaining women and men/boys and girls in trials in the local context, have they proposed a strategy for gathering such information in the process of conducting the trial, or integrated such questions in preparatory research?

Enrollment:

- Do informed consent processes consider women's limited autonomy in decision-making in contexts where that is a concern, and provide the necessary support, materials, time and opportunity for them to consult with others if they wish to?

- In trials for children, does the consent/assent process consider women's autonomy to assent to their child's participation?

Retention:

- Have they proposed gender-specific retention strategies that consider knowledge of local gender roles and gender-related barriers to adherence (e.g. whether women in the study want to use the product; whether there is social stigma within the community affecting women's adherence to the product)?

- If the trial aims to recruit populations that are marginalized or stigmatized, or that require specialized recruitment and retention strategies, has the grantee demonstrated willingness and readiness to partner with community-based organizations who are well-equipped to engage these populations respectfully and with the appropriate consideration?

Adherence:

- Have they demonstrated a good understanding of potential gender-related barriers to product-use adherence (where applicable) and adherence to study requirements such as attending clinic visits; and have they proposed strategies to better understand and/or address them?

- If the trial requires or encourages contraceptive use, have they made efforts to remove access barriers such as bringing services on-site? If so, are they offering a full range of modern contraceptives using informed choice counseling? If referral to off-site services is necessary, are they evaluating the quality of services available and creating strong referral mechanisms?

SOCIAL IMPACT OF PARTICIPATION

1. How will you ensure that benefits and risks of participation accrue equitably to men/women (boys/girls)?

2. How will you assess, document and address social harms[5] that may occur due to trial participation such as stigma and discrimination or gender-based violence?

3. Will the trial include other key populations that may experience high levels of stigma and discrimination (e.g. MSM, transgender, sex workers)? What concerns might you expect related to ethical/good public health and development practice and how will you address them?

What to look for in grantee responses on social impact of participation (examples):

- Do they demonstrate an understanding of the potential social impact of participation, as well as from a gender perspective?

- Have they proposed gender-specific strategies to limit any potential negative social impact of participation; to detect, document and report social harms; and to provide services on-site or through referral to address them? Have they assessed staff capacity to do so?

- Have they involved or established partnerships with individuals/organizations with appropriate expertise and tools to ensure that the trial protects the rights of key populations?

ANALYSIS

1. If you will recruit both men and women, please describe your plan for sex-disaggregated data analysis and reporting in line with the foundation's open access and data access policies.

2. If the trial is not powered to detect sex differences, how will you conduct subgroup analysis to identify clinically meaningful sex differences in safety, efficacy/effectiveness?

What to look for in grantee responses on analysis (examples):

- Is the plan for subgroup analysis sound? Would it successfully identify any emerging trends?

- Is there a plan to publish or disseminate sex-disaggregated data and analysis, even if findings are not statistically significant? (Refer to https://bmgf.sharepoint.com/sites/foundationpolicies/Policies/Open%20Access.docx)

ENDNOTES

1. Refers to trials of products that are not specific to one sex or products where inclusion of both sexes is not otherwise justified by scientific rationale

2. Refers to trials of products that are not specific to one sex or products where inclusion of both sexes is not otherwise justified by scientific rationale

3. The job aid is based on research undertaken by the foundation as part of an Internal Gender Challenge. Outputs of that work include two position statements (for internal use) that summarize the evidence, and four case studies that illustrate how sex and gender can impact clinical trials.

4. Low literacy may also affect men as well as women; however, in many contexts women have lower literacy rates than men.

5. Social harms are unintended negative consequences of participation in clinical trials.