MESSAGE

Medical Science Sex and Gender Equity

Accounting for sex and gender in biomedical, health and care research

A policy framework for research funders

April 2024

The George Institute for Global Health UK

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Policy contents

Introduction

We all have a responsibility to ensure that the research we fund and conduct is rigorous, reproducible and beneficial to all.

Sex and gender play fundamental roles in a person's experience of health and illness, influencing:

Limited accounting for sex and gender dimensions in biomedical, health and care research leads to gaps in the evidence base which translate into worse clinical outcomes for all people.

We therefore expect that funding applications and funded research will account for sex and gender dimensions throughout the research cycle, including the recruitment/procurement of participants/subjects, the data collected, the analyses conducted, and the results reported. Applications and research which do not meet this expectation must provide a strong, evidence-based justification for not doing so.

This policy sets out our expectations of applications for research funding, and offers guidance for researchers on how to meet these expectations. This policy applies to pre-clinical, clinical and population health research, covering both quantitative and qualitative studies.

More detailed guidance on integrating sex and gender in research is available on the Medical Science Sex and Gender Equity (MESSAGE) website.

A note on terminology

Throughout the policy, we refer to **sex "and/or" gender**. Although we acknowledge that the terms "sex" and "gender" are used in different ways in different contexts, here we will use them as terms with distinct meanings that are explained in detail in Section 2. We will use the term "sex" to refer to biological characteristics, and "gender" to refer to aspects of a person's identity. This policy encourages researchers to be precise about which sex and/or gender characteristic(s) they need to account for to answer their research question.

We use the term **"subjects"** to refer to any entity on which pre-clinical research is conducted, including cells, tissues, organs or animals. We use **"participants"** to refer to people with whom clinical and population health research is conducted. We use the acronym **I/VSC** to refer to participants who are **intersex/have variations of sex characteristics**.

Pre-clinical researchers should specify the sex characteristics of research subjects they will account for in their proposed study design. We expect researchers working with human participants – referred to here as **"clinical and population health"** studies – to consider whether information on sex or gender characteristics, or both, are needed to answer their research question, to justify this in their application, and to propose a study design that reflects this choice.

By **"integrating"** or **"accounting for"** sex and gender, we mean that research critically considers, is appropriately designed for, and transparently reports on the sex and gender dimensions of its participants/subjects. Implicit in this is being clear about and justifying when sex and/or gender have not been accounted for.

"Sex- and/or gender-disaggregated analysis" refers to the analysis and presentation of data separated by sex and/or gender.

Section 1: Centring sex and/or gender dimensions

We expect that:

Pre-clinical research includes a representative sample with regard to the sexes that make up the affected population and conducts sex-disaggregated analysis.

Clinical and population health research includes a representative sample with regard to the sexes and/or genders that make up the affected population and conducts sex- and/or gender-disaggregated analysis.

The sex and/or gender distribution of the sample can be representative of the general population, the population with the disease/condition of interest, or a target population within the disease/condition population, depending on what is most appropriate to answer the research question. See Section 3b for more details.

For clinical and population health research: The choice whether to account for the sex and/or gender of participants should be made based on what is most appropriate to answer the research question. More information about these variables can be found in Section 2 of this policy.

NB Clinical and population health research accounting for sex should include a representative sample of female and male participants and, where possible, I/VSC participants.

Clinical and population health research accounting for gender should include a representative sample of cisgender women/girls and men/boys and, where possible, trans and non-binary people. **Proactive effort should be made to include trans, non-binary and I/VSC participants.**

We expect funding applications to include a description of:

1. Which sex and/or gender characteristic(s) will be considered and accounted for, and which research participants/subjects will be included to reflect these characteristic(s).

   For clinical and population health research: Include a description of why the study will account for sex or gender or both to answer the research question.

2. The target distribution of participants/subjects by sex and/or gender and why this distribution has been selected to answer the research question.

3. *For clinical and population health research:* For research involving primary data collection, planned strategies for recruiting and retaining the target sex and/or gender distribution of participants. For research involving the use of secondary data, a description of the sex and/or gender distribution of participants in the original dataset.

   For pre-clinical research: Planned actions for procuring, managing and storing/housing the target sex distribution of subjects. For research involving the use of secondary data, a description of the sex distribution of subjects in the original dataset.

4. An analysis plan, including details of any planned sex- and/or gender-disaggregated analysis. If researchers are not planning to perform a sex- and/or gender-disaggregated analysis, they must explain why.

In instances where a research proposal does not address one or more of these expectations, a strong, evidence-based justification must be given for why it is not considered necessary. Further guidance on (in)appropriate justifications can be found in Section 3a.

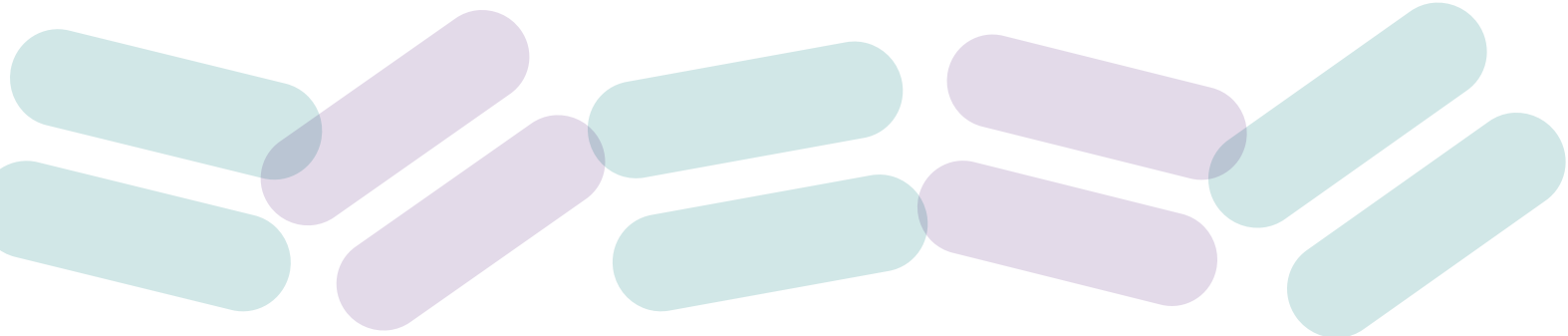
Please note that for **quantitative studies,** it is not a mandatory expectation of this policy for researchers to design every study to have adequate power to detect statistically significant results in each and every sex or gender group, nor to identify a statistically significant sex and/or gender difference. Even where sex and/or gender findings are not statistically significant – either due to there being no true difference or an inadequate sample size to detect a difference – reporting of data and findings by sex and/or gender is essential for supporting future research – including meta–analyses – of clinical relevance.

We expect **published outputs** to always include transparent information about the sex and/or gender distribution of the study sample and to report sex- and/or gender-disaggregated summary statistics. This is irrespective of whether sex- and gender-disaggregated statistical analyses have been conducted, and irrespective of whether sex and/or gender differences have been identified. Further information on accounting for sex and gender in research outputs can be found in Section 3f.

We strongly encourage researchers to include individuals of different sexes and/or genders in patient and public involvement and engagement activities.

We recognise that researchers using **secondary data** may be restricted in their ability to appropriately account for sex and/or gender because of limitations in existing datasets. Nonetheless, we expect applications to describe the sex and/or gender distribution of participants in the original dataset and to relate this back to the sex and/or gender distribution in the population of interest. All other expectations in points 1-4 above apply.

The quality of the integration of sex and/or gender dimensions in the research proposal will be taken into consideration during the application review process.



Section 2: How are we using the terms "sex" and "gender"?

Sex and gender are multi-faceted concepts which are used and understood differently in different contexts, societies, groups and languages. Usage of these terms has changed over time and is likely to continue changing. This policy's recommended usage of these terms aims to facilitate biomedical, health and care research that is rigorous, reproducible and beneficial to all.

In this policy, we use sex and gender as terms which each encapsulate multiple characteristics that have relevance to health and illness. It is important that researchers have a precise understanding of which specific sex and/or gender characteristic(s) are relevant for their research question and the affected population. **To meet our policy expectations, researchers must justify the sex and/or gender characteristic(s) they will account for and specify the research participants/subjects from whom they plan to collect data to reflect these characteristic(s).**

Researchers do not need to account for all sex and/or gender characteristics, and some characteristics will be accounted for more often than others. Characteristics other than those suggested below will be considered when a strong justification for doing so is given.

Under this policy, pre-clinical researchers will be concerned with sex characteristics, while clinical and population health researchers will be concerned with sex and/or gender characteristics.

In this policy, **sex** refers to the biological attributes which differentiate females and males, and which can include variations of what are considered female-typical and male-typical characteristics (sometimes known as "variations in sex characteristics" or "intersex").

When considering sex for the purposes of research, the characteristics of subjects and participants which researchers may need to account for include:

- Sex chromosomes
- Gene expression
- Hormone profile[1]
- Secondary sex characteristics
- Internal reproductive organs
- External reproductive organs

NB For most people, data on external reproductive organs is recorded at birth and determines a person's documented sex or "sex assigned at birth" [2]. In many datasets, sex is only recorded as "sex assigned at birth". Researchers should always report which sex and/or gender characteristic(s) the study accounts for and should clearly state if sex was determined using the "sex assigned at birth" classification.

1. Depending on the research question, it may be relevant to account for both endogenous and exogenous hormones when accounting for this characteristic.
2. It should be noted that some people's sex assigned at birth may differ from the presentation of their external reproductive organs ,for example if they have undergone gender-affirming surgery. Similarly, I/VSC people may have been assigned a sex at birthwhich is not relevant to all of their sex characteristics. A person's documented sex can also differ from the sex of their biological characteristics.

In this policy, **gender** refers to an aspect of a person's identity. A person is subjected to a range of social forces (both constraints and privileges) based on their gender, which may influence their behaviours, their perception of themselves and how they are treated by others. All of these influences may be relevant for biomedical, health and care research. When accounting for gender, it is worth keeping in mind that an individual's gender exists on a spectrum, can change over time, and intersects with other aspects of their identity such as age, ethnicity and sexual orientation. There is considerable diversity in how people experience and express gender within and across societies.

When considering gender for the purposes of research, the characteristics of participants which researchers may need to account for include:

- Gender identity (the gender with which a person identifies)
- Gender expression (how a person outwardly presents themselves in relation to gendered forces)
- Gender modality (whether a person's gender identity is the same as their sex assigned at birth or not, i.e. whether they are cisgender or transgender)
- Perceived or presumed gender (how a person's gender is typically understood by those around them, which may differ from their gender identity and/or gender expression)

Further information on these definitions and how to collect sex and gender data can be found on the MESSAGE website.

Section 3: Guidance for researchers

This policy will ensure that research is designed, conducted, and reported in a way that enhances scientific rigour and reproducibility. It is our priority to support researchers to meet our policy expectations and we welcome feedback. Our expectations will evolve over time in response to this feedback and developments in the field.

We encourage researchers to read the more detailed guidance on the MESSAGE website.

3a. There may be appropriate justifications for focusing on single-sex or single-gender characteristic(s) in study design.

We may still fund research that accounts for characteristics that are specific to one sex ("single-sex characteristics") or one gender ("single-gender characteristics") where a strong justification for doing so is provided in the research proposal.

Examples of cases where this may be appropriate include:

- Research on conditions or experiences specific to single-sex or single-gender characteristic(s) [3].
- Research aimed at redressing historic sex and/or gender bias, and/or gaps in the evidence base.
- Research into the mechanisms of purely molecular interactions (for example, when investigating protein-protein interactions) or microorganisms which do not have a sex.
- Research using cells or tissues whose sex cannot be ascertained.[4]
- Research where the availability of only acutely small sample sizes mean that data are only available on single-sex or single-gender characteristics (for example, participants with rare conditions or limited samples held in tissue banks).[5]
- Research where access to data about sex and/or gender characteristics has been predetermined by the limitations of the dataset (for example, when using databases or tissue banks which have not collected this data)[6] .

Other evidence-based justifications for conducting research that is specific to single-sex or single-gender characteristic(s) will be considered as part of the peer review process.

3. In clinical and population health research, participants' sex may differ from their gender. It may be relevant for researchers to account for people of different genders even if you are accounting for single-sex characteristic(s) or vice versa.

4. Pre-clinical researchers should ensure they have legal and ethical permission before trying to determine sex themselves and must act in accordance with the Material Transfer Agreement so as not to breach patient anonymity.

5. Please note that in this instance, researchers should still report the sex and/or gender distribution of participants/subjects in research outputs.

6. Please note that any newly proposed databases or tissue banks will hitherto be assessed according to this policy.

In most cases, the following will not be sufficient justification for excluding participants/subjects that are specific one sex and/or gender. Strong justifications for such exclusions may be taken into consideration.

- Prior work, including pilot studies, has only accounted for with single-sex or single-gender characteristic(s), with no justification for doing so.
- Hormone variations, including hormone variability in female participants/subjects across the oestrous cycle or life course, or in any participants/subjects as a result of hormone replacement therapy.[7]
- Pre-clinical researchers do not currently know the sex of the subjects used, but it is possible to find this out (see footnote 4).
- There is a lack of evidence of sex and/or gender having an effect on the condition or experience, or existing evidence shows there is no sex and/or gender effect.

3b. The target sex and/or gender distribution of research participants/subjects should be designed to answer the research question.

This policy does not expect one particular distribution of research participants/subjects on the basis of sex and/or gender. Instead, researchers should consider and justify what a suitable distribution of research participants/subjects should be to answer their research question.

In some studies, it may be more relevant for the sample to represent the sex and/or gender split in the general population; in others it may be more relevant for the sample to represent the sex and/or gender split in the population with the disease or condition, or a sub-set of that population. The decision of which population to account for may depend on the accuracy of past estimations of the sex and/or gender split for the disease or condition.

For clinical and population health studies: This policy recognises that in practice it is not always possible to recruit and retain the number of participants of each sex and/or gender to meet the planned distribution. Nonetheless, we expect researchers to describe the strategies they will take to recruit proactively and work to retain under-represented groups, such as cis women and girls and trans, non-binary and I/VSC people.

3c. The size of samples should be designed to answer the research question and should be tailored to the study type.

Application of this policy does not necessarily lead to an increase in sample sizes. We strongly encourage researchers to consider what sample size they need for each sex and/or gender to answer the research question and meet the expectations of this policy regarding sex and/or gender distribution.

For quantitative studies: Please note this policy is not an expectation that research will be designed to produce statistically significant results for each sex and/or gender group, nor to identify statistically significant sex and/or gender differences. However, researchers are strongly encouraged to compare results by sex and/or gender group, estimating between-group differences and limits of accuracy in such estimation. Interpretation of differences, or lack of them, should be discussed.

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7. This policy does not expect researchers to account for exogenous hormones (including from contraception), the different stages of the oestrous cycle, or hormone changes in females across the life course (including prepubescence, puberty, pregnancy and menopause). However, depending on the research question, there may be scientific value in examining these factors in more detail.

3d. Our primary concern is to fund research that constitutes good value for money.

We recognise that applicants may be concerned about study costs related to accounting for sex and gender. During the review process, it is our priority to assess whether an application constitutes good value for money. This means we will compare the scientific quality and rigour of the proposed study with the proposed costs.

Researchers can make changes to research practice to meet the expectations of this policy without necessarily incurring expenses. Some actions to this end are listed in Section 3e.

3e. Research that has already been funded should strive to integrate sex and/or gender wherever possible.

We encourage current grant holders to explore ways to integrate sex and/or gender throughout the remaining stages of their grant period to make their research more generalisable

This could include, but is not limited to:

- Reading and reflecting on the literature on sex and/or gender differences in the field.
- Conducting relevant sex- and/or gender-disaggregated analyses.
- Accounting for sex and gender when reporting research findings (see guidance in Section 3f).
- Reflecting on lessons learned about how to account for sex and gender, such as (in)effective recruitment/procurement strategies or innovative analytical methods.
- Identifying areas for future research to explore sex and/or gender dimensions further.

3f. Published outputs should be transparent about whether sex and/or gender have been accounted for or not.

Published outputs should adhere to the following steps to improve transparency about whether and how sex and/or gender dimensions have been integrated:

- **In the Title,** if participants/subjects of only one sex and/or gender were included, specify this.
- **In the Abstract,** consider if it would be valuable to describe the main sex- and/or gender-specific findings that were identified or to state that none were found.

- ***In the Introduction/Background section:***

» Describe known sex and/or gender differences in the field, or sex and/or gender gaps in the evidence base.

» In literature reviews, cite relevant evidence about sex and/or gender dimensions in the field.

- ***In the Methods section:***

» Describe which sex and/or gender characteristic(s) were accounted for and why.

» Describe the sex and/or gender distribution of the sample and the rationale for this selection (including if the study accounted for only a single-sex or single-gender characteristic(s)).

» Give details of sex- and/or gender-disaggregated analyses conducted or state that none were conducted.

- ***In the Results section:***

» Describe the sex and/or gender distribution of the sample.

» Report summary data disaggregated by sex and/or gender.[8]

» Report all findings of sex- and/or gender-disaggregated analyses, irrespective of whether a difference has been observed. Sex and/or gender differences (or the absence thereof) should be quantified, together with appropriate measures of uncertainty.

» Be sure to always report null findings of sex- and/or gender-disaggregated analyses.

- ***In the Discussion:***

» Describe how the findings relate to the wider literature about sex and/or gender in the field (including if no sex and/or gender differences were found).

» Point to areas regarding sex and gender where the research indicates further study would be valuable.

» If the planned sex and/or gender distribution was not recruited or retained, give details of this and offer an explanation as to why.

» Do not present research conducted on, or primarily on, a specific sex and gender group as generalisable to all populations. For example, a study conducted only or primarily on males should not be presented as a relevant to all participants/subjects.

» When reporting strengths and limitations, include a reflection on how well the research has accounted for sex and/or gender, why that was the case, and identify areas which could be improved upon.

- ***In Supplementary Materials:***

» Include sex- and/or gender-disaggregated summary data and findings wherever their inclusion in the main text has not been possible.

The framework for this policy was co-designed by representatives from the UK biomedical, health and care research sector, including funders, regulators, publishers, people with lived experience and researchers, as part of the MESSAGE Policy Lab series (2023-24). We welcome feedback.

8. Sex- and/or gender-disaggregated analysis should not be reported on if this will compromise anonymity of participants due to sample sizes being very small.

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Cite this policy:

MESSAGE Writing Group, Witt A, Woodward M, Jenkins K, Jenkins B, Hockham C, Peters S, Politis M, Cooper L, Pow R, Norton R & Womersley K. (2024). *Accounting for sex and gender in biomedical, health and care research: A policy framework for UK research funders.* Medical Science Sex and Gender Equity.

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