



MESSAGE

Medical Science Sex and Gender Equity

Co-designing best practice: Refining a sex and gender policy framework for UK biomedical, health and care research funders

Policy Lab 2 - 27th September 2023

How to use this report

This report sets out the **feedback from participants at the second MESSAGE Policy Lab** on the Draft MESSAGE Policy Framework. Images of key sections of the draft Framework can be found in this pack **alongside the relevant feedback**.

Relevant feedback has been used to revise the draft Framework. **The final MESSAGE Policy Framework will be disseminated in Spring 2024.**

We thank all Policy Lab participants for sharing their thoughts and expertise and for their continued engagement in the MESSAGE Policy Lab process.

This report was written by Alice Witt, Kate Womersley, Marina Politis and Louise Cooper. The design was by Anshu Manchanda.

General

Framing considerations

- Policy should be written in **accessible language**
- Ensure policy requirements are built around the definitions of sex and gender and that there is **consistency** throughout
- Researchers need **reassurance** that increased costs for sample size inflation will not penalise them
- The benefits of the policy for fostering **better science and health equity**, rectifying historic **gaps in the evidence base**, and bringing **economic benefits** should be explained
- Be clear that accounting for diversity is also part of putting in an application that is **competitive**
- Integrate a **life course** element throughout, including in the policy requirement
- Different sections will be relevant to **quantitative or qualitative research**
- Information at the start should explain why the policy describes studying “**sex and/or gender**” and what “**integrating**” or “**accounting for**” s/g means

Wording considerations

- Use “**participants**” instead of “subjects” (the latter is dehumanising)
 - research “**with**” not “on” participants
 - “study people” changed to “**include** people”
- Use “**conditions**” or “**disorders**” instead of “diseases” (the policy scope is wider than disease)
- Make sure the wording throughout is inclusive of **children**
- One suggestion that the policy should refer to “sex **and** gender”, not “sex **and/or** gender”
- Be explicit about how **trans people** fit into the policy requirements
- Preference for “**variations of sex characteristics**” over “intersex” or “differences of sex development”. Can say “**...sometimes referred to as intersex**”, but intersex is an identity and not everyone identifies with this.
 - Intersex is not a “third sex” and is not one single thing. Guidance will need to clarify how to account for the wide range of variations that occur across different sex characteristics.
- Should **avoid reference to the binary**. Avoid saying “both sexes” and “biological sex”, and use “sex characteristics” or “sex assigned at birth” rather than “sex”
- Suggestion to describe sex and gender as “**variables**”

1. Choosing the policy requirement – Wording and content

Policy title

Feedback on Option 1

Caution about the word “**inclusive**”

- Some feel the implication is too political, has connotations of being too “woke”
- Others feel it is aspirational but unattainable, and may make this policy seem like an optional add-on/unrealistic

Recognition this would allow for development of policies relating to **other areas of diversity**

- However, not confident that other guidance regarding race and ethnicity will be made

General considerations

- Frame the policy in terms of “**science**” or “**research**”
- Include the term “**best practice**” or “**excellence**”
- Remove the term - or go beyond - “**design**”
- One suggestion that “UK research” sounds **parochial**
- One suggestion to mention “**lifecourse**”

0.1 **Title option 1: Inclusive design in UK research: sex and gender dimensions**

Title option 2: Accounting for sex and gender in UK research design

Title option 3: Free text...

Title suggestions

- Combine the first half of both – “Inclusive design in UK research: accounting for sex and gender” (or vice versa)
- “Equitable evidence: a policy framework for sex and gender in UK research design”
- “Scientific/Research accuracy and reproducibility: Sex and gender reporting”
- “Research accuracy and health equity: sex and gender reporting”
- “Addressing sex and gender dimensions in UK research”
- “Generating evidence that for sex and gender dimensions: a framework for UK research”
- “Sex and gender in research design”

Policy requirement wording

Preferences were split between whether the policy should “**expect**” or “**require**” stipulations around sex and gender.

- 0.2 We **encourage/expect/require/insist** all research applicants to consider the biological and sociocultural attributes of sex and/or gender in their research. Sex and/or gender should be included in the design, methods and analyses, interpretation, and dissemination of findings of all research, when appropriate.
- 0.3 We **encourage/expect/require/insist** studies involving cells and tissues (animal or human), and animals to include female and male sexes in the design of experiments and conduct a sex-based analysis. Studies involving humans should **include people of diverse sexes and/or genders** and carry out a sex- and/or gender-based analysis by default.

General considerations

- “Encourage” considered **too weak**
- “Insist” considered **too strong**, setting a bad tone
- Suggestion that “consider” is not **strong enough**, so should be used in conjunction with something stronger - “require” or “insist”
- Suggestion para 0.2 uses “require”, para 0.3 uses “expect”. Another suggestion para 0.2 uses “require”, para 0.3 uses “insist”.

Expect

- Considered **firm** but not aggressive
- The policy should be followed by wording later in the framework to make it clear what the levers are to get people to **comply**
- Should be accompanied by “**where possible**” or “**unless justified**”

Require

- There may be **legal implications** of this term
- Concern something mandatory would be **too challenging to implement** from the outset due to practical limitations, being at different stages of this process etc.
- This strength of wording could end up creating a **two-tier system** between funders with bigger budgets who can afford to adopt mandatory requirements (and therefore produce higher-quality research) and smaller funders who cannot.

Policy requirement

General considerations

- Consider splitting into **pre-clinical and clinical** guidance
- Consider how wording should differ between **RCTs** and other types of studies
- Emphasis on the need for transparency about the integration of s/g being a **strength or a limitation**
- Don't say “**drawing on relevant literature**” – unclear what to do if literature doesn't exist and could give too much leeway
- Unsure if funders can **monitor published outputs** and question having a policy which can't be monitored. Could this part be a recommendation rather than policy?

- 1.3 We expect researchers to include in their applications **(Which of the below should be included? Should anything else be added?):²**
 1. The planned distribution of subjects by sex and/or gender.
 2. The rationale for the planned distribution of subjects, drawing on relevant literature.
 3. The proposed outreach activities to recruit the planned distribution of subjects, drawing on relevant literature.
 4. An analysis plan, including details on how sex and/or gender differences will be examined.
- 1.4 In instances where a researcher does not plan to account for sex and/or gender dimensions, a strong justification, drawing on relevant literature, must be given.
- 1.5 We expect researchers' published outputs to include **(Which of the below should be included? Should anything else be added?):³**
 1. A description in the Methods section of the sex and/or gender distribution of the sample and the rationale for this selection. Where only one sex or gender is used, the justification for this decision must be explained.
 2. Any study findings which indicate a sex and/or gender difference.
 3. Mention in the Limitations section of any weaknesses in study design related to sex and/or gender considerations, including stating when such considerations are not taken into account.
 4. Data disaggregated by sex and/or gender in supplementary materials.

Policy requirement - Expectations for applications

- 1.3 We expect researchers to include in their applications **(Which of the below should be included? Should anything else be added?):²**
1. The planned distribution of subjects by sex and/or gender.
 2. The rationale for the planned distribution of subjects, drawing on relevant literature.
 3. The proposed outreach activities to recruit the planned distribution of subjects, drawing on relevant literature.
 4. An analysis plan, including details on how sex and/or gender differences will be examined.

General considerations

Point 1: Add how the planned distribution is relevant to the research

Point 2: What if there is a lack of evidence/literature to draw on?

Point 3: Beyond outreach activities, talk about wider strategies for inclusive recruitment such as broad inclusion criteria, minimising in-person follow-up visits etc.

Point 4: Concern that the requirement to include an analysis plan suggests the priority is looking at s/g differences, when it is actually to estimate a generalisable effect and assess whether the effect depends on s/g.

Expectations to add

- Should include rationale for why researcher chose to collect data on **sex and/or gender**
- Should include mention of s/g in **literature reviews**, including the current **breakdowns of diagnosis** of the condition by s/g when available
 - If researchers have done research before, they should give the breakdown of s/g in that previous research – or clarify if it didn't previously look at s/g
- Should include **outputs management plan** on reporting
- Ask about **retention**, not just recruitment
- Ask about plans for **ethical approvals** for clinical work
- Ask **how data on s/g will be measured** and collected

Policy requirement - Expectations for published outputs

General considerations

Point 1: Add how s/g data was measured and collected

Point 2: Make clear that the policy does not require every study to look for statistically significant s/g differences

Point 2: Clarify that finding no differences is also an important outcome that should be reported too

Point 2: Clarify that the s/g outcomes that publications describe should be biologically relevant

Point 4: Add that disaggregated data should also be included in the main manuscript when relevant. Putting them in the supplementary materials is the bare minimum. (However, some journals have limits to what can go in supplementary materials so don't want to restrict where researchers are able to publish)

Point 4: Clarify that data should not be disaggregated if that would risk de-anonymising participants (e.g. small numbers of sex- or gender-diverse people)

1.5 We expect researchers' published outputs to include **(Which of the below should be included? Should anything else be added?)**:³

1. A description in the Methods section of the sex and/or gender distribution of the sample and the rationale for this selection. Where only one sex or gender is used, the justification for this decision must be explained.
2. Any study findings which indicate a sex and/or gender difference.
3. Mention in the Limitations section of any weaknesses in study design related to sex and/or gender considerations, including stating when such considerations are not taken into account.
4. Data disaggregated by sex and/or gender in supplementary materials.

Expectations to add

- Give detail of s/g dimensions in the **title**, where appropriate
- Give detail of s/g dimensions in the **Abstract**
- **Literature reviews** should cover existing literature on s/g
- **Discussion** of s/g findings (or lack of) and their relevance for the field (in relation to existing literature)
- If planned s/g distribution was **not recruited or retained**, explanation of why
- Areas for **further research** relating to s/g findings (or lack thereof)

Wording to describe inclusion of people in research

General considerations

- This section should depend on the policy's **overall definitions** of sex and gender
- **No consensus** on one option being best, though most preference for Option **1 or 4**
- Include the qualification “**where appropriate**” throughout
- Don't use “**human**” - this is dehumanising
- Use very **specific language** – e.g. trans women/men, people with VSCs
- Emphasis should not only be on inclusion but **quality inclusion** (e.g. best practice for data collection) and **transparency**
- Must clarify that this policy is about increasing the diversity of the group studied, **not a pick-and-choose list**

1.2 From DD MM 2024, [organisation name] **requires** that researchers study:

- Both sexes in cells, tissues and animals.
- **Option 1:** Diverse sexes and/or genders in humans.
- **Option 2:** Female, male and (where possible) **intersex** people and/or women, men and (where possible) gender diverse people.
- **Option 3:** Women and men and/or females and males in human studies. Efforts should be made to study people with variations in sex characteristics and/or diverse gender identities.
- **Option 4:** In humans: females, males, people with variations in sex characteristics, women, men, and/or gender diverse people.

Suggestions

- Separate out **sex characteristics, gender and gender modality**. These things are related but it is useful to separate them for the sake of precision.
- An alternative could be: “If you plan to **exclude** any category, you must justify it”

Wording to describe inclusion of people in human research

General considerations

Option 1

- This works as long as there are clear definitions of who it is referring refers to
- Expand to include “intersex people with VSCs” or “Humans with different sex variables and representing different genders”

Option 2

- Guidance on how to collect this data will be essential
- Too easy to opt out

Option 3

- Confusing to have women, men, males and females in the same sentence
- Makes it too easy to exclude trans/intersex people
- Too category-focused

Option 4

- Use specific terms such as “trans man/woman”, as many people do not understand the difference between “woman” and “female”, for example
- Too category-focused

1.2 From DD MM 2024, [organisation name] requires that researchers study:

- Both sexes in cells, tissues and animals.
- **Option 1:** Diverse sexes and/or genders in humans.
- **Option 2:** Female, male and (where possible) intersex people and/or women, men and (where possible) gender diverse people.
- **Option 3:** Women and men and/or females and males in human studies. Efforts should be made to study people with variations in sex characteristics and/or diverse gender identities.
- **Option 4:** In humans: females, males, people with variations in sex characteristics, women, men, and/or gender diverse people.

Suggestions

- “Humans with different sex variables and representing different genders”
- “In humans, with appropriate [attention to/accounting of] sex characteristics and gender dimensions as it pertains to the study question and affected populations”
- “Females and males in human studies. Efforts should be made to include people with VSCs and/or diverse gender identities”
- “In human studies: Female, male and (where possible) people with VSCs, women, men and (where possible) gender diverse people”

Impact on the likelihood of an application being funded

General considerations

- Preference for **Option 4, then 3**
 - Feeling that Option 4 is what we should be aiming for, but need phased progression to get there (1 -> 3 -> 4)
- The **quality** element is important. How do you measure quality?
 - Does “quality” refer to how much consideration has been paid to include s/g into the experimental design? The quality of the implementation of the design? The quality of the data outcomes?
- Better to focus on how this will lead to **better applications** which are more likely to be funded rather than saying it’s an automatic fail if applicant doesn’t adhere
- Concerns that making this a mandatory requirement will create a **two-tier system** between funders with larger and smaller budgets
- Funders need **more time** to agree this, and possibly **space to adapt wording** based on the nature of each funding call
- Funders may not be able to commit to “**will**” as assessment is by **committee members or external reviewers** who variably engage with current review form questions on how diversity dimensions have been included

1.5 **Option 1:** Integration of sex and/or gender considerations will increase the likelihood of an application being funded.

Option 2: Integration of sex and/or gender considerations will increase the likelihood of an application being funded. Applications which do not engage with the sex and/or gender question will not progress further.

Option 3: The quality of the integration of sex and/or gender dimensions will affect the likelihood of an application being funded.

Option 4: The quality of the integration of sex and/or gender dimensions will affect the likelihood of an application being funded. Applications which do not engage with the sex and/or gender question will not progress further.⁴

Suggestions

- Could wording say “**to be considered for funding**”, rather than reference to likelihood of being funded? E.g. “To be considered for funding, applicants are expected to account for sex and/or gender characteristics”
- “The quality of the integration of sex and/or gender dimensions will affect the **competitiveness** of the application”
- Use wording “the **quality** of research design that integrates sex and gender dimensions”
- “**Engage**” is good wording, but is it enforceable or monitorable?

Policy scope

1.7 This policy applies to both quantitative and qualitative research.⁵ (Y/N)

- Total consensus that **both qualitative and quantitative research** should be included
- Recognition that **guidance for qual and quant studies will be different**, and the existing policy is quant-focused
 - Sex- and gender-stratified analysis may not be relevant for some qualitative studies so the focus should be more on being transparent when reporting findings, not generalising findings in one sex and/or gender to the whole population, and encouraging researchers to be reflexive about sex and/or gender.
- Suggestion that **PPIE activities** should also come under the remit of this policy too, as this is important for ensuring the study as a whole is sex- and/or gender-sensitive and produces high-quality data

2. Choosing definitions – Two options

Definitions – General

General considerations

- **Lots of interest in a characteristics approach**, but overall feeling that a **mixture** of category and characteristics will be needed
 - And that this definition would need to be supported by detailed materials about **how to practically translate definitions into data collection practices**
- Need definitions which **allow for evolution** as understanding about s/g progresses - a characteristics approach is good for this
 - One suggestion that researchers could **present their own definitions**, as long as they justify them adequately - the focus of the requirement bring more on transparency
- Should explain the difference between biological and **legal/documentated sex**
- Emphasise need for **standardised reporting** of sex and gender to minimise research waste. Recognition that current reporting (based on a category approach) isn't always correct and rigorous, e.g. often no systematic process for accurately collecting s/g data on trans and non-binary people.
- Definitions should come at the **start of the policy**, or in a **glossary** at the start. Suggestion to highlight key points in the policy and put the rest of the detail in appendices, for the sake of concision.

Considerations for definition wording

- Describing gender as “**sociocultural**” won't be clear or accessible to researchers
 - Concern that this term doesn't give individuals autonomy to define their gender
- Strong feeling that sentence about gender **intersecting** with other characteristics should be included
- Several suggestions to bring out gender **identity**, gender **modality** and gender **expression** as gender characteristics
- Suggestion to emphasise that gender is a **continuous variable**
- Make sure **children** are represented throughout (girl, boy, gender non-conforming)
- Highlight that **sex and gender intersect** – a person's sex can affect their gender identity
- Sex can change over time, is fluid (e.g. hormone changes) – focus should be on “**bell curves not boxes**”

Category approach

- 2.2.1 In this policy:
- 2.2.2 'Sex' refers to the biological attributes of humans and animals that differentiate female, male and intersex (also referred to as **Differences in Sex Development**), including chromosomes, gene expression, hormone levels and function, reproductive organs and different molecular expressions at cell level.⁸ The categories of sex are usually female and male, but there is variation in the presentation of different biological components of sex.⁹
- 2.2.3 **Option 1 (Gender):** 'Gender' is distinct from sex, and refers **to the attribution of behaviours, expectations and roles to different sexes** in humans, therefore varies over time and by social and cultural context. Gender is **often regarded as binary** (for instance, woman or man), however there is diversity in how individuals and groups experience and express gender (such as gender fluid, non-binary).¹⁰
- 2.2.4 **Option 2 (Gender):** Gender refers to the socially-constructed roles, behaviours, and identities of girls, women, boys, men, and non-binary and gender diverse people. It influences how people perceive themselves and each other, how they interact, and the distribution of power and resources in society.¹¹ Gender attitudes and behaviours are complex and change through time and in place. Importantly, gender is diverse, fluid, multidimensional and intersects with other categories, such as sex, age, socioeconomic status, sexual orientation and ethnicity.¹²
- 2.2.5 It is important that biomedical, health and care researchers have a robust understanding of which sex and/or gender attributes are relevant for their study so they can select appropriate research subjects.
- 2.2.6 Data collection on sex should include the options:
- Female and Male for cell, tissue and animal studies.
 - Female, Male, and **Person with variations in sex characteristics/differences of sex development/Intersex** as a minimum for human studies.¹³
- 2.2.7 Data collection on gender (in human studies) should include the options Woman, Man, and Non-binary as a minimum.¹⁴
- 2.2.8 Further information about definitions and how to collect sex and gender data can be found **here**.¹⁵

Characteristics approach

- 2.3.1 In the UK, 'sex' is conventionally understood as pertaining to biological characteristics and 'gender' as pertaining to sociocultural features. Gendered features are shaped by a society's norms and a person's internal connection to a gendered category **such as woman, man or non-binary**.¹⁶
- 2.3.2 Biological sex can be classed as female, male or **intersex**. **Intersex** individuals have variations or combinations of what are considered XX female-typical and XY male-typical chromosomal, gonadal and genital sex characteristics.¹⁷
- 2.3.3 A person's gender exists on a spectrum,¹⁸ can be fluid,¹⁹ and intersects with other characteristics such as age and ethnicity.²⁰ There is therefore considerable diversity in how individuals and groups experience and express gender.²¹
- 2.3.4 In this policy, we use 'sex' and 'gender' as single terms which each encapsulate multiple characteristics that have relevance for health and disease. It is important that researchers have a robust understanding of which sex and gender characteristics are relevant for their study so they can select appropriate research subjects. Researchers must be able to justify their selection of research subjects based on the characteristic(s) selected to study.
- 2.3.5 Sex characteristics include:²²
- External reproductive organs
 - Hormone profile
 - Internal reproductive organs
 - Secondary sex characteristics
 - Chromosome profile
 - **Sex assigned at birth**
- 2.3.6 Gender characteristics include:²³
- Self-identity
 - Social role (as determined by gender norms)
 - Character traits (as determined by gender norms)
 - Behaviours (as determined by gender norms)
 - Social relationships (as determined by gender norms)
- 2.3.7 Further information on the meaning of these characteristics and their applicability in data collection can be found **here**.²⁴ Data collection on sex and gender characteristics should include options which account for variations beyond a female/male or woman/man binary.
- 2.3.8 Further information about definitions and how to collect sex and gender data can be found **here**.²⁵

Definitions – Category vs Characteristics

	Category	Characteristics
Pros	<ul style="list-style-type: none">• Data is easier to collect	<ul style="list-style-type: none">• More precise• More sustainable and less research waste• Shifts focus from being political to scientific• Allows more scope for evolution of terms over time
Cons	<ul style="list-style-type: none">• Categories may exclude some people, or group people inaccurately• Leads to dichotomies rather than nuance and detail• May have to be re-done in a few years as this approach is likely to be bypassed as thinking progresses• People may be falsely categorised• Categories which are defined differently may be compared across studies	<ul style="list-style-type: none">• May be difficult for researchers to understand who they need to collect data from• Some existing databases don't break down in this way• Concern about meta-analyses, as results may still be reported differently between researchers based on how they aggregate/cluster small numbers

Definitions – Characteristics

- The introductory paragraph should clarify that **sex is more than 'sex assigned at birth'**
 - Some suggestion to remove 'sex assigned at birth' from list of sex characteristics, as it is the same as external genitalia and is just an administrative decision made a long time ago
 - However, recognition that '**sex assigned at birth' is used in secondary/existing data** (cohorts, data linkage, healthcare records)
 - Emphasis that it is the transparency that is important. So. using 'sex assigned at birth' as a metric is fine, as long as this is clear.
- Strong conflicting opinions on whether “a person’s **internal connection to a gendered category**” should be used in definition of gender but more opinions that it shouldn’t be included – concerns that using the word “category” is confusing
- Suggestion to emphasise that **sex characteristics are not always only male or female**
- Suggestion to clarify that sex characteristics may change over the **lifecourse**, and those changes may be relevant for data collection
 - It may be relevant to clarify how the research is categorising **endogenous vs exogenous** hormones
 - It may be relevant to clarify or select whether a female participant is **pre- or post-menopausal**
 - It may be relevant to clarify or select what stage of the **oestrous cycle** female participants are in
- Clarify that researchers don’t need to look at every characteristic, but just consider which is **most relevant**. And that some characteristics will be used **more than others** (e.g. most people don’t know their chromosomal make-up, so it may not be helpful to ask for it).
- Policy should emphasise that selection of characteristics should be “**As relevant to the research question and affected populations**”
- One suggestion this should be part of **educational materials**, rather than policy

Definitions – Guidance

- Researchers will need examples of how to apply the characteristics approach to **different types of research**
 - Context is key: the characteristics to use will change based on the research question; the questions that are best to ask will change depending on the study they are applied to
- Questions on sex should ask first about sex, then ask if their sex is the same as their 'sex assigned at birth'
- Guidance needs to cover **data analysis based on characteristics**, as well as data collection
- Guidance should be clear about how this approach will apply to **meta-analyses**, particularly for gender characteristics
- Suggestion that data collection can use **umbrella terms** such as “non-binary” or “gender-diverse” to encapsulate people who have a more specific term for their sex and/or gender identity, but which could be grouped together for the purpose of visibility within (and analysis of) data
- Some suggested it would be useful to **collect a variety of data at the start of the study** to make sure you can learn the most possible (for example an unexpected sex or gender trend)
 - However, others highlighted that researchers must be mindful of **GDPR requirements** to only ask participants about their sex/gender when relevant to the research question
- Guidance should encourage researchers to see that **previous research is not necessarily best practice**
- Researchers must be clear to ask participants about **specific characteristics**, rather than just asking about their sex or gender in general and assuming that that answer is **applicable to every characteristic**

3. Choosing guidance for researchers – Sections and content

Guidance – Section 3a

General considerations

- This section **should be included**, but needs to be worded in a way that doesn't allow leeway or opportunities for illegitimate excuses
- These bullets need to be aligned with the policy's definitions - including placing the focus on sex characteristics
- One suggestion to add requirements about the **effect of contraception**
- One suggestion to consider offering guidance about studying females who are different stages of the **oestrous cycle**
- One suggestion to include guidance on how **embryos** fit into this policy

Unacceptable justifications

- Be more explicit about what is being referred to by **hormonal variations**
 - Mention pregnancy, menopause, puberty
 - Mention how hormonal variations influence trans and intersex people
- One suggestion to **remove the first bullet point** as it is not always possible to know the sex of cells. This also contrasts with guidance that it is an acceptable justification to exclude immortalised cell lines.

- 3.1 a. There may be appropriate reasons not to account for sex and gender in study design. (Y/N. If Y, what is missing?)**
- 3.1.1 We may still fund single-sex or single-gender studies where there is strong justification in your research proposal for doing so. Cases where the use of a single sex or gender may be appropriate include:
- Diseases or mechanisms relating to a single sex characteristic (for example, ovarian cancer).²⁷
 - Diseases or phenomena specific to the experiences of people of a single sex and/or gender.²⁸
 - Research into the mechanisms of purely molecular interactions (for example, when investigating protein-protein interactions).²⁹
 - Research using immortalised cell lines.³⁰
 - Instances where there are acutely scarce resources (for example, human tissue samples of rare diseases).³¹
 - **Where costs would be excessive (for example, several times higher than a single-sex or single-gender study).**³²
- 3.1.2 Other reasons for conducting research in a single sex or gender will be considered as part of the peer review process. These may include scientific, logistical, or ethical considerations.³³
- 3.1.3 In most cases, the following will not be sufficient justification for excluding a sex or gender: **(Which of the below should be included, and what else should be added)**
- You do not know the sex of the cells, tissues or animals you use.³⁴
 - Your existing knowledge of the literature does not include sex and gender considerations in your field.
 - There is a lack of evidence of sex or gender having an effect on the disease, mechanism or phenomenon.³⁵
 - Prior work, including pilot studies, has been performed in only one sex or gender.³⁶
 - Hormonal variations, including hormonal variability in female subjects across the menstrual cycle or as a result of hormonal replacement therapy.³⁷

Guidance – Section 3a

Appropriate justifications

- Strong consensus to **remove “where costs would be “excessive”**
 - Lack of clarity or consensus on what constitutes excessive costs
 - This is for funders to judge, not researchers
- Several suggestions that the first bullet point should be removed
 - Strong feeling that **ovarian cancer is not a useful example** - can also affect trans men and intersex people. Also men pass on genes associated with it so would need to be included in genome-wide associated studies.
- Must consider that a **single-sex study could include people of multiple genders**
- Add that research studies can study a single sex or gender if they are aimed at **remedying an existing data gap** because of historic exclusion from research (e.g. CVD in women)
 - Also areas where research has **historically been limited** (e.g. endometriosis)
- Add a specific justification for when there is a **small disease population** (i.e. rare conditions), where only one sex/gender may be available
- Add a justification on **when factors are out of the applicant’s control**, such as limited databases or tissue banks
- Add a justification on **when sex cannot be determined** in your experimental model (e.g. in some developmental biology studies)
- Mention that **when there is evidence** that sex/gender has an effect of diseases, studying in only one sex/gender may be justification

3.1 a. There may be appropriate reasons not to account for sex and gender in study design. (Y/N. If Y, what is missing?)

- 3.1.1 We may still fund single-sex or single-gender studies where there is strong justification in your research proposal for doing so. Cases where the use of a single sex or gender may be appropriate include:
- Diseases or mechanisms relating to a single sex characteristic (for example, ovarian cancer).²⁷
 - Diseases or phenomena specific to the experiences of people of a single sex and/or gender.²⁸
 - Research into the mechanisms of purely molecular interactions (for example, when investigating protein-protein interactions).²⁹
 - Research using immortalised cell lines.³⁰
 - Instances where there are acutely scarce resources (for example, human tissue samples of rare diseases).³¹
 - **Where costs would be excessive (for example, several times higher than a single-sex or single-gender study).**³²
- 3.1.2 Other reasons for conducting research in a single sex or gender will be considered as part of the peer review process. These may include scientific, logistical, or ethical considerations.³³

Guidance – Section 3b

- 3.2 b. Whether sample sizes need to increase or not depends on the type of research you conduct. (Y/N)**
- 3.2.1 b. (i) Cell, tissue or animal studies**
- 3.2.2 By using multifactorial statistical analysis, some studies can meet this policy requirement using the same or only modest increases in sample size. However, sample sizes may need to be increased in some instances.³⁸
- 3.2.3 You should include details of your expected sample size and planned distribution by sex in your study design and analysis plan.³⁹ Relevant considerations for this decision-making process include:⁴⁰
- If the study is exploratory or experimental in design.
 - If the study needs to be powered to be statistically significant for both sexes.
- 3.2.4 You can learn more about multifactorial statistical analysis [here](#)⁴¹.
- 3.2.5 b. (ii) Human studies**
- 3.2.6 It may be more difficult to use multifactorial statistical analysis in human studies than animal or cell studies. Where it is not possible, **and in some other circumstances**, sample sizes may need to be increased.
- 3.2.7 You should include details of your expected sample size and planned distribution by sex and/or gender in your study design and analysis plan.⁴² Relevant considerations for this decision-making process include:⁴³
- If the study is exploratory or experimental in design.
 - If the study needs to be powered to be statistically significant for both sexes.
- 3.2.4 You can learn more about statistical methods for human studies [here](#)⁴⁴. You can find out more about ways to reduce additional costs [here](#).⁴⁵

General considerations

- Uncertainty whether this section should be included and if the content is accurate – existing **knowledge is contested**. This might be better in guidance only.
 - Response that it is **hard to provide one-size-fits-all guidance** to a wide range of studies and researchers should know enough about stats not to need this.
 - This should be **assessed by reviewers** and the policy shouldn't give a specific steer
- Need to explain **how this relates to definitions** of sex and gender (especially the characteristics approach) and how that works in terms of **meta-analyses**
- Statistical **power** must be mentioned – but clarify that the policy is not requiring every study to be powered for each sex/gender
 - Clarify that under-powered stratified analyses can be valuable, especially for future research and meta-analyses
 - Clarify that it will rarely be possible to power studies to produce significant results for trans and intersex populations. For these populations, more emphasis needs to be placed on achieving sufficient sample sizes.

- One suggestion wording should **encourage researchers to increase sample size** to broaden and enhance their research so we learn more about the sex and gender aspects of the research
- Guidance must be clear that looking at sex and/or gender differences doesn't just mean splitting the dataset into s/g groups and comparing findings, researchers also must demonstrate that there is an **interaction between s/g and the treatment effect**

Guidance – Section 3b

Some parts of this guidance will be more or less relevant for **clinical or pre-clinical research**

Considerations for pre-clinical research

- Guidance depends on whether a study is *in vivo or in vitro*
- Good to mention **multifactorial analysis** for cell/animal research and worth drawing on MRC resources on this
- Question on what the guidance should be for **intersex cells**
 - Likewise for trans people's cells where hormones may have led to changes in sex over time
- There are issues around historical biases in the existing models. Specific funding will be needed for validating models to be relevant for different sexes and genders
- Concern that “only modest increases in size” is not clear - what is modest for some may not be for others

Considerations for clinical research

- This guidance might be misread as saying studies should always be powered for a comparison between sexes/genders, so this should be clarified
- This guidance may need to be broken down further to reflect different types of studies and phases
- May need to mention that changes to sample size will need to be balanced with the feasibility of recruiting a diverse group
 - There are legitimate reasons it might not be possible to increase sample size, such as costs, number of eligible people in UK, limitations on number of study sites

Guidance – Section 3c

General considerations

- Strong feeling that **the current wording of this guidance cannot be included** in the policy framework
 - The degree to which funders can cover costs is **at the discretion of individual funders**. For some, funding caps may be an issue
 - Section could be included but would need to be worded **ambiguously**
 - Section could be included but should focus more on **acknowledging there will be changes to costs**, rather than stating those costs will be covered
- Strong feeling that the discussion on costs of accounting for sex and gender is **not about “additional” costs** because these costs are not additional if they are **necessary** for doing good quality research. Instead, the focus should be more on **“value for money”**.
 - Wording could say **“costs must be justified”** or focus on **“appropriate costs”**
 - Funders will need to discuss and decide if they want to fund more studies which are of poorer quality, or perhaps fewer studies that are more scientifically rigorous and benefit more members of society
- **Examples and evidence** about the expected increase in costs needed to account for sex and gender would be helpful
- Other costs to mention are **compensation** for participants, resources to recruit participants from **overlooked populations**, and costs associated with additional **data processing and analysis** (especially for qualitative studies)
- Costs for **training** researchers should be kept in the policy wording

3.3 c. Additional costs when accounting for sex and/or gender dimensions **will** be covered. (Y/N)

3.3.1 For some studies, increasing sample sizes may lead to extra costs, including but not limited to:

- Additional animal housing.
- Additional compensation for participants.
- Additional recruitment or PPIE activities.
- **Training for researchers.**

3.3.2 **Additional costs to meet the requirements of this policy will not affect the likelihood of an application being funded.**

3.3.3 Many actions to meet the requirements of this policy do not necessitate additional expense. These actions are listed in section (e) as actions and can also be taken by existing grant holders.⁴⁶

Guidance – Section 3d

General considerations

- Feeling that **this section should be included** but lack of consensus on what the guidance should say
 - Some feel that distribution should be based on disease population
 - Others feel that researchers should aspire for a distribution based on the population as a whole, to **not perpetuate data gaps**
 - This is particularly important when there is **limited/potentially incorrect data about distributions** in the disease population (e.g. historically it was believed that ADHD was much more prevalent in men/boys due to limited research)
- One suggestion that this section should be tailored for **different study types**
- Some feeling that this section should be mentioned **earlier in the policy** and that this would resolve many of researchers' concerns

3.4 d. The planned distribution of research subjects should be tailored to the needs of the study design. (Y/N)

3.4.1 This policy does not require one particular distribution of research subjects on the basis of sex and/or gender (e.g. 50% women and 50% men). In some studies, it may be more relevant for the sample to represent the sex and/or gender split in the population as a whole, and in others it may be more relevant for the sample to represent the sex and/or gender split in the disease population.⁴⁷ Decisions on sample size split should take into consideration the statistical methods that will be used to analyse the data.

3.4.2 You should consider the rationale for your planned distribution and reflect this in your study design and analysis plan. In human studies, **you should take proactive steps to include sex and/or gender diverse research subjects wherever possible.**

You can find more information about planning your sample distribution **here**.⁴⁸

- Mention that saying “50% women, 50% men” **perpetuates the binary**, is archaic and raises heckles, detracting from the key point
- For some conditions, proactive steps may need to be taken to **redress historic under-representation** of certain groups in sample distributions
- Policy should emphasise that researchers must take proactive steps to “**retain**” as well as recruit diverse populations (e.g. women are less likely remain in a trial so extra efforts are needed to retain them)
- This part of the policy should be explicit that researchers should take **proactive steps to include transgender participants**

Guidance – Section 3e

General considerations

- A few suggestions **to not include this section in the policy itself**, but rather as wider guidance or principles
 - This section is **only applicable at the point of policy implementation** – it's no longer relevant when researchers apply for more money, as they will be subject to the rest of the policy
- But several participants felt that **encouraging existing grantees to incorporate the policy's principles** is important
 - Regardless of initial study design, **publications** from studies that have already been funded can account for sex and gender
- Recommendation to use **guidance for funders** to add **prods** for each of these throughout the application process
- Components to add include:
 - Acknowledging how s/g are accounted for in the **Strengths and Limitations** section
 - Reflecting on **lessons learned** and how the research could have been adapted to better account for sex and gender
- This section should mention that as this policy is rolled out, not engaging with this guidance **may affect publications' acceptance and future funding**

e. This policy will not apply to research that has already been funded or for applications which have already been submitted. (Y/N)

We encourage existing grant holders to explore ways to integrate sex and/or gender considerations throughout the remaining stages of their grant period to make their research more generalisable.⁴⁹

This could include, but is not limited to, the following:

- Familiarising yourself with the literature on sex and/or gender differences in your field.
- Developing methods to disaggregate study data by sex and/or gender.
- Conducting sex- and/or gender-based analysis on study data.
- Describing the sex and/or gender distribution of the sample and the rationale for this selection in paper Methods.
- Acknowledging sex and/or gender differences and not presenting research conducted only on male subjects/men as applicable to all subjects/people.
- Reporting findings that indicate similarities and/or differences between sexes and/or genders.
- Acknowledging when data has not been sex- and/or gender-disaggregated as a limitation of the research.
- Publishing data disaggregated by sex and/or gender in supplementary materials.
- Identifying areas for future research to explore sex and/or gender dimensions further.



Thank you for reading this report.

You can find out more information about the MESSAGE project at www.messageproject.co.uk or on X at [@MESSAGE_TGI](https://twitter.com/MESSAGE_TGI)

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