

# Sex Inclusive Research Framework (SIRF): an evaluation tool to assess whether an in vivo research proposal follows the sex - inclusive research philosophy.

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## Abstract

A new, interactive framework supports the evaluation of in vivo and ex vivo research proposals from a sex inclusive research perspective delivering a traffic light classification, indicating whether a proposal is appropriate, risky, or insufficient with regards to sex inclusion. This tool is designed for use by researchers, (animal) ethical review boards, and funders to generate a rigorous and reproducible assessment of sex inclusion at the proposal level, thus helping address the embedded sex bias in preclinical research.

## Why is there a need for a decision framework to assess the sex inclusion position of research proposals?

Within preclinical research, there is an endemic and persistent sex bias whereby research is predominately conducted with a single sex, typically male animals or male cell lines (1-3). This can result in our fundamental biological knowledge being biased (4). To redress this imbalance and improve the translation of scientific findings between humans and other animals, numerous funding bodies have released inclusion mandates (5, 6) that require the automatic inclusion of both sexes unless strong justification is provided.

To date, these policies do not require scientists to study differences between males and females *per se*, but instead aim to improve the generalisability of studies by taking sex into consideration in the design and statistical analysis. This can be achieved by estimating from both sexes an average intervention effect and by visualising and analysing data in such a way that if there is a large sex difference in the intervention effect this will be detected. For funders, regulators or ethical review bodies to apply these policies in a systematic and consistent manner, there is a need for resources to help assess whether a research proposal is compliant with sex inclusive mandates. Not only do scientists struggle to include both sexes (1-3), but when data from both sexes are collected there is

often unequal representation (7) and inappropriate visualisation and analysis of the data (8, 9). It is therefore important to not only encourage balanced inclusion but also appropriate analysis.

Research has shown that scientists are generally supportive of sex as an important biological variable but there are barriers to implementing sex inclusive designs (10, 11). Frequently, the cited barriers are culturally embedded misconceptions. These include the mistaken perspectives that females are inherently more variable (12, 13), that sex differences will introduce variability in the data decreasing statistical sensitivity (14), or that studying both sexes will increase the number of animals needed (10, 11) and hence the cost (15). Some researchers have identified logistic/welfare concerns (for example the need for single housing to reduce male mouse aggression)(15). Fear of change is also a factor, that has been identified as preventing a change to the status quo (10).

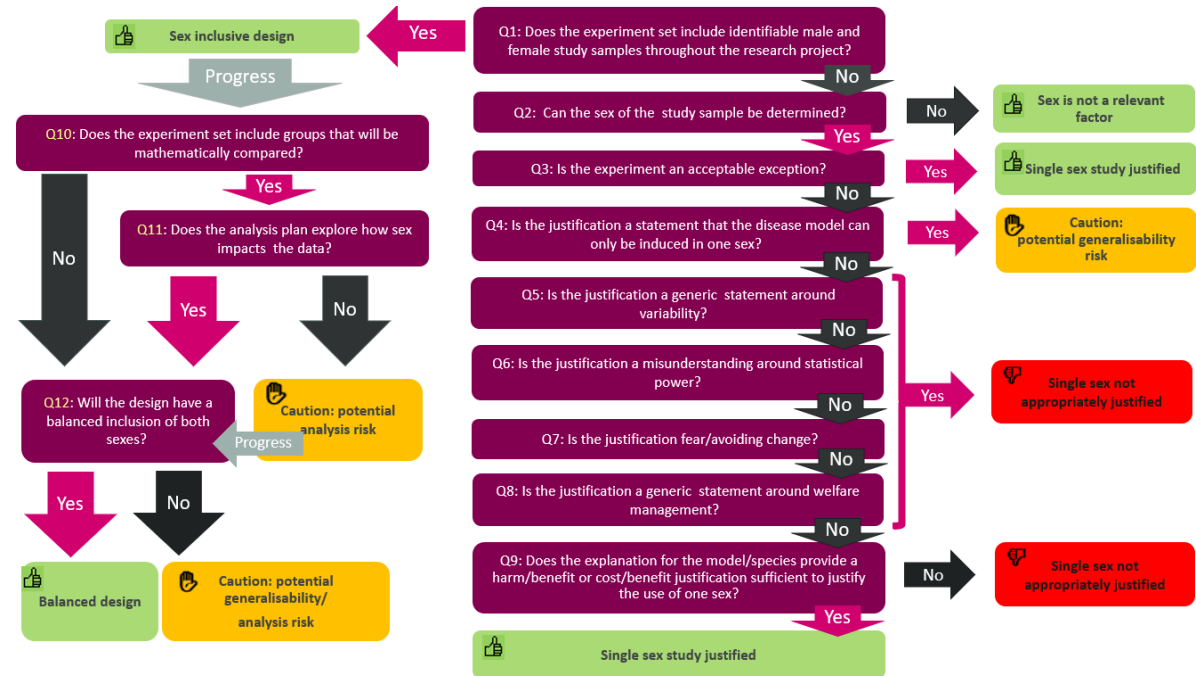
Here we present a framework to rapidly assess an in vivo or ex vivo research proposal to determine whether the proposal is sex inclusive, balanced and whether analysis plans have included sex. When a proposal includes only a single sex, the framework evaluates whether the justification is a scientifically appropriate and a reflective assessment that is not based on common misconceptions. The framework fulfils multiple objectives: (1) to provide transparency in the assessment process for both researchers and those evaluating the proposals, thus aligning expectations, (2) to deliver reproducible and unbiased evaluation of the proposal, and (3) to help address common misconceptions, thus encouraging considered justifications that will enable a better understanding of when sex inclusive research is possible.

## The Sex Inclusive Research Framework

An original decision tree concept was initiated and developed by a working group of community leaders, including representatives from industry, academia, ethical review committees and funding review communities (**Figure 1**). In addition to the decision tree, detailed supporting information for each question consisting of assessment advice and why the question was included is provided. This

framework has been tested in a grant review cycle by a reviewing panel and by several UK-based ethics review boards.

The framework can be executed via a pdf document or alternatively via an interactive web interface. The interface returns a report which can be submitted alongside the research proposal to the assessment body. To support the use of the framework (Supplementary 1 – SIRF document version), the website contains supporting information including a recorded seminar on the framework, FAQs (Supplementary 2 - SIRF FAQs), and some example classifications from a published dataset of single sex justifications (Supplementary 2 – Evaluation justification dataset).



**Figure 1: The Sex Inclusive Research Framework decision tree.**

Underpinning the Sex Inclusive Research Framework is a decision tree consisting of twelve questions which, when applied to a research proposal, results in the assignment of one or more traffic light outcome classification indicating whether a proposal is appropriate, carries some risk or insufficient with regards to sex inclusion.

## Limitations of the framework

The present framework was developed to support the evaluation of *in vivo* or *ex vivo* research proposals. If a proposal contains multiple sets of experiments, then the framework needs to be independently applied to each. Adaption or the development of a separate framework is being considered for *in vitro* research projects and will need development with a different set of stakeholders.

The framework provides a structured set of questions to evaluate a proposal. However, many of the questions require a subjective evaluation, which could lead to variations in the judgement reached. The provision of supporting information for each question should mitigate that risk. Furthermore, decisions for a question may shift in time as science/culture evolve. For example, different communities might have a different ability to identify the sex of a sample when genetic testing might be required, due to access to appropriate technology and the associated costs. This could move the classification from one where the single sex is not appropriately justified to appropriately justified when considering a cost/benefit evaluation.

## Implementation of the framework

Effective implementation of sex inclusive research policies requires regulatory bodies to provide training and guidance for applicants and evaluators (16). This framework aligns with this need by providing a knowledge-base and practical support for the implementation of sex inclusive research policies with a system openly accessible to staff, applicants and evaluators.

The framework may be used in several ways. Researchers could use the framework before submitting a proposal or application to evaluate their position in a manner consistent with how it will be evaluated by a funding panel or ethical review body. Research funding bodies or ethical review body assessors could independently evaluate research proposals, either with the PDF format or through the

web tool. Alternatively, the assessors could request that applicants submit a report as evidence of the applicant's assessment of their justification and review the classification provided.

The assessing bodies will need to explore the applicability of the framework to their specific area. For example, the framework includes a question on whether the design has equal representation. If the information is not collected during the application process, even in a situation where both sexes are included; warnings might accumulate around the analysis or design. There are several options for the assessing body: proceed with this potential risk, request additional information, adapt the decision tree for their application process, or adapt the application process. An assessment of national funding agencies sex, gender and diversity analysis policies, concluded that funders should provide applicants and evaluators similar forms and instructions for consistency across the research process (16). This framework could help provide a consistent evaluation for efficient engagement by the research community.

## Conclusions

Through this initiative, we aim to support the research community in using both sexes in the design and analysis of preclinical experiments by providing a framework to differentiate genuine barriers preventing the use of both sexes from culturally embedded misconceptions. Cultural change is necessary to make sex inclusive research the standard for scientific rigor, excellence, and combating sex bias in biomedical research.

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