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Claire Newland
Director of Policy Ethics and Governance
Medical Research Council
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Dear Claire,

I'm writing to you regarding the recent announcement that the Medical Research Council will now expect both sexes of animals, tissues and (non-immortalised) cells to be used as default in research proposals. Having previously highlighted the importance of recognising sex as an experimental variable in response to the Government's consultation on its Women's Health Strategy¹, the Academy is very much supportive of this move as a direction of travel. Your report has also prompted us to consider as an Academy how we should adjust our own policies in our role as a funder ourselves.

We have consulted with a number of our Fellows and grant awardees about these new policies. Those we contacted were similarly supportive of this move by MRC, with a consensus that sex is an important risk factor and variable that contributes to a number of different biological processes and disorders. We noted that elsewhere, government bodies such as the United States' National Institutions of Health, and some journals already have these requirements in place.²

Some areas of potential consideration for implementing this policy were also offered to us. As the Academy is keen to support you to implement these new policies in the most effective way possible, we would like to highlight some of these areas raised, along with some suggested mitigations. I am also grateful for your kind offer to meet with Academy staff to explore further the impact of these new proposals.

Increased cost of compliance

A common thread in our conversations was the potential for (possibly substantial) increases in costs of delivering research projects. In particular, due to the single-housing requirements of male animals due to aggressive behaviour and the larger known variability in female animals, the new proposals would lead to more cages being needed for each experiment. Depending on how animal facilities charge researchers for their animal work, this could result in considerable additional animal and staff costs. We note that guidance exists to mitigate some of these factors, but the experience of researchers already in this position was that such increases could still arise.

Given these potential increases in the cost of research in the above scenarios using both sexes, further clarification and assurances from UKRI's prior indication that they are willing to consider these factors in the duration and costing of grants would be very much welcomed.

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¹ <https://acmedsci.ac.uk/file-download/22836484>

² <https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable>

Mitigating the potential for unequal impact of these new requirements on different institutions

Relatedly, there was a concern that the financial and logistical implications of this policy could result in only the better-resourced institutions being able to fully comply with the new proposals.

For example, an increase in cage number in order to comply with this policy may pose particular challenges for research groups with limited space in their facilities. A collaborative approach from MRC, maintaining an awareness of and working with institutions likely to be most affected could encourage greater compliance.

New training requirements

We also heard that some researchers may be concerned they will need more complicated experimental design and analysis, adding additional time to each experiment. This is difficult to manage when on a timed PhD program, for example. However, this challenge could be mitigated if, as UKRI guidelines suggest, males and females can be analysed separately and not as pooled datasets. This simplifies analysis and enables an assessment of whether sex-based differences exist in the study and their relevance.

With appropriate statistical design and analysis, this increased variability in data and more complex design can be accounted for and may lead to results that are more reliable. However, researchers may need more access to training and resources to enable them to make the best use of statistical design tools.

Many such resources do already exist, such as the National Centre for the Replacement, Refinement and Reduction of Animals in Research's Experimental Design Assistant online tool.³ The uptake of, and access to, these tools and resources should therefore be more widely encouraged and promoted alongside the new policy.

Another area in which careful communication, engagement, and/or further training could have an important role is around the potential for increased numbers of animals. We were reminded by Fellows that there can be a tendency of researchers to interpret the "reduction" arm of the "3Rs" principles as using the lowest number of animals possible, but this is of course a misconception. Reduction refers to the use of the smallest group size needed to get robust and reliable results. When sex is considered as a biological variable, then more animals may be required to get sufficient data, while still meeting the 3Rs requirements.

Training must also be provided to ensure high standards of welfare as single-housing also has welfare implications if running a long-term experiment. In these cases, researchers have preferred the use of females, or have found using both sexes difficult to manage and may benefit from access to resources on ensuring high welfare in these instances.

In addition to the above, the Academy would be supportive of MRC considering options to provide its own guidance, feedback, or training for applications, to assist applicants to design experiments better to both minimise costs and meet new requirements. This additional element of support could also help mitigate the uneven impact of these requirements on differently resourced institutions.

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Communication and engagement

Given annual reporting of the number of animals used in research each year, MRC should therefore consider a careful approach to communicating and explaining any changes to the media and public in overall numbers used. We also hope that perceived or real implications for the 3Rs have been considered as part of any consultations with the Home Office and ASRU.

That said, it was also suggested to us that breeding programmes may in fact become more efficient and researchers may gain more data from their investment if both male and female littermates are used. It could be that the new proposals will, for example, encourage researchers to set up breeding programmes that generate the mouse genotypes they need from single pairs and use resulting pups of both sexes.

Other considerations

Implementation of this policy will also affect research using donated tissues, and some researchers noted that there may be particular challenges for those working with material of human origin. For example, researchers using blood that is donated anonymously may not have access to information on the sex of the donor. Meanwhile, research into conditions more likely to occur in one sex for cultural and/or behavioural reasons, including studies into HIV and among men who have sex with men may also need to be considered.

Following these proposals, we hope reporting of sex as a variable when creating new biobanks and datasets will be encouraged, in turn enabling researchers to ask questions about sex-based differences when they might not have been able to before.

I appreciate that you are still fully developing these policies, and deepening your engagement with other organisations and researchers. As these conversations continue, we would encourage MRC to share learnings and best practice with other funders and supporters of health research, so that that we can work collectively as a sector to improve our approach to sex as a biological variable. I hope the points raised here provide a helpful input to this process, and for the important work MRC is carrying out in this area.

Yours sincerely,



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