

with situations like this so that committee members can be better equipped to handle future requests of this nature.

1. Clayton, J.A. & Collins, F.S. NIH to balance sex in cell and animal studies. *Nature* **509**, 282–283 (2014).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* 8th edn. (National Academies Press, Washington, DC, 2011).

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RESPONSE

Before the amendment

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Any member of the IACUC may request full committee review of a protocol according to the Animal Welfare Act and Regulations (AWARs) (§2.31)¹; therefore, Myles is within her rights to bring this to full committee. Although not generally considered the realm of the IACUC, the AWARs (§ 2.31)¹ also state that the protocol should contain “a rationale for involving animals and appropriateness of species and numbers to be used.” Thus, the committee can question the researcher regarding the appropriateness of the sex and numbers to be used.

When full committee review is requested, the AWARs (§ 2.31)¹ stipulate how the review must occur (*i.e.*, “at a convened meeting of a quorum of the IACUC”) but not when this must occur. The IACUC chairman could, at his discretion, convene an IACUC meeting prior to the usual date to discuss this protocol. However, we feel that Rothman could pursue other approaches that would potentially negate the need for the amendment in the first place.

In recent years, there has been a greater emphasis on investigating potential sex differences. Rothman was specifically questioned on the use of females only and evidently provided a strong scientific justification for not using males that was accepted by Myles during the initial review; we do not believe that the manuscript reviewer’s *prima facie* recommendation for redoing the study with males requires that it be redone. If the argument provided by Rothman was persuasive enough for Myles

then it may also be sufficient to satisfy the manuscript reviewer. Before submitting an amendment, Rothman should respond to the reviewer with the same scientific argument regarding the use of females that he used during his initial IACUC submission. While a reviewer can recommend that an experiment be done, this does not mean that the manuscript would be rejected if a valid scientific argument is provided against performing the additional experiment. Rothman could also provide a rationale for the use of females only within the manuscript as another way to demonstrate that the use of males was considered and rejected on scientific grounds. The ethical use of animals demands that they only be used when absolutely necessary, so Rothman would be remiss if he did not explore ways that the study could be accepted for publication without using additional animals.

If the above approach was unsuccessful, Rothman could ask the journal for an extension to resubmit the paper so that the full IACUC would have time to review the amendment.

In order to better address situations like this, we believe the IACUC would benefit from formulating a consistent policy strongly encouraging the use of both male and female animals unless scientifically justified. They should also determine whether a manuscript reviewer’s recommendation alone is justification for emergency consideration of additional animal experiments.

1. Animal Welfare Act regulations. 9 CFR, Chapter I, Subchapter A.

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RESPONSE

More work upfront to avoid last minute problems

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The researcher had previously justified the need to use only female rabbits in the study. It is absolutely reasonable for the IACUC

reviewer to request full committee review (FCR) since the modification to the protocol contradicts the original request by the IACUC reviewer for the PI to consider both sexes. Physiologic variation due to sex is a known influence in many types of experiments. Recent NIH guidance regarding “Consideration of Sex as a Biological Variable in NIH-funded Research” requests that scientists evaluate the potential role of gender as a variable in studies which use vertebrate animals¹. Although this guidance was set to be effective for NIH applications starting in late January 2016, Great Eastern University does not indicate if Rothman’s work was funded after the guidance date, nor, in fact, if it was NIH funded. Prior to initial approval by the IACUC, Rothman was asked by the IACUC reviewer to provide justification for the use of female rabbits only. According to the IACUC, Rothman provided sufficient evidence supporting the concerns that the results were independent of the influence of the sex of the animal.

The IACUC chair cited federal regulations preventing an expedited processing of the protocol, however, the IACUC chair did have the ability to call for an off-cycle full committee meeting to discuss the modification request. As per the “Guide for the Care and Use of Laboratory Animals” (*The Guide*), the committee “must meet as often as necessary to fulfill its responsibilities”². Facilitation of a timely review could have been met through this method. This may have allowed for a review that would meet the publication deadline if the IACUC felt like the researcher now provided adequate justification for additional animals.

Requiring additional experimentation is a common necessity during manuscript review. Rothman has the opportunity to respond to the reviewer’s concern during the resubmission of the manuscript. It seems entirely plausible that if the researcher has scientific evidence that specifies the research results would not be affected by the sex of the animal, this should be taken into account by the manuscript reviewer and editor. Initially, Rothman provided sufficient scientific justification/evidence to the IACUC reviewer as to why the use of a single sex was appropriate for the study. It would be presumed that the reviewer would be able to accept this scientific justification if it were placed in the manuscript or in a