

Author's Commentary on "Counting Sheep: Ethical Protocols in Animal Research"

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Background: The concept of proper and ethical treatment of research animals

Rules and regulations for animal research are derived from various laws, including the Animal Welfare Act (CFR 1985) (enforced by the Animal and Plant Health Inspection Service, a branch of the USDA); the Public Health Service's Policy on Humane Care and Use of Laboratory Animals (PHS 1996); and any state and local laws that may apply. Guidelines for research protocols are taken from the *Guide for the Care and Use of Laboratory Animals*, commonly known as "the Guide" (National Research Council 1996). The Guide is a collaborative effort between the Institute of Laboratory Animal Resources, the Commission on Life Sciences and the National Research Council. Institutional committees typically use the Guide as a reference when reviewing research protocols that involve animal use.

An animal care and use protocol (ACUP) is a document that gives the working details and justification for a research project. These details might include the number of animals involved, techniques used during surgical procedures, the names of the people who will be performing procedures, what medications will be administered (i.e., anesthetics, experimental drugs, analgesics), and what form of euthanasia (if appropriate) will be used. In order for a project to proceed, the ACUP must be reviewed and approved by the institutional animal care and use committee (IACUC). Only those approved items listed in the ACUP are allowed, and any changes to the protocol must be authorized before they can be instituted. (National Research Council 1996, pp.10-11)

The investigators, the animal care personnel and the attending veterinarian are encouraged to work together to avoid and deal with problems as they arise. However, allegations of noncompliance with established animal care and use rules at an institution if serious, can warrant an investigation by an IACUC-established Investigative Committee. Anyone can report to the IACUC. The Investigative Committee's response after investigation will depend on the findings of the inquiry and legal and institutional policy that the IACUC is bound by. The IACUC can suspend research, and if the research was supported by PHS funding, the suspension must be reported to the PHS. (National Institutes of Health 1992, D-1 -- D-3)

In recent years, there has been increasing public awareness of animal use in research. This area of the field of bioethics has therefore become more prominent (Baker and Mellor 1993, pp. i-iii) As a consequence, researchers using animal subjects are held to stricter standards today than were common in the past. This increasing accountability of scientists for their actions regarding animal subjects has been achieved in a number of different ways. Reputable research institutions have formed committees that are responsible for overseeing the approval of research protocols (i.e. the IACUC mentioned above). Other factors that have helped improve the lot of research animals include accreditation of animal facilities in order to have common standards of care and housing. Ideally, these changes should have decreased redundancy in animal use (less "waste" of animals). (Novak and Hitleberg 1989, p.14) They also delineated limits on the number and type of procedures that can be performed and called for better standards of living for the subjects. In practice, of course, the ideal is not always realized.

In reviewing bioethics cases, one should keep in mind the difference between what could be considered cases involving basic ethical flaws and those cases in which there may be violations in what would otherwise be thought of as useful, justifiable research. For example, the former could be a situation in which research is not justifiable in terms of its results and has the potential to abuse the animals used. In such cases the basic foundation of the project is flawed. In the case presented here, the research has already been approved; therefore we can assume that the review committee felt that the research was justifiable and the use of the sheep model appropriate. Thus, initially at least, the reader is not asked to make a decision regarding the ethical appropriateness of the research but whether certain ethical issues arise in the course of the research.

The foremost issue that this particular case will raise for most readers involves the ethics of using animals in biomedical research. While this case was not written with the intention of focusing on this aspect of bioethics, it is an important concept and should be addressed. Research on animals is usually conducted under the assumption that pain and suffering in subject animals should be avoided, but that there will be certain cases in which the information that can be gathered from the research will have great positive impact on future directions in human medicine. In these cases most people consider that the research must still take place.

In this case, Mariel is a junior graduate student working on a collaborative project that involves detailed animal surgery. Since she is not a veterinarian, she cannot do the procedures herself; instead, she relies on Jorge Beliz, collaborator and fellow graduate student.

As the case develops, it becomes apparent that Mariel is being placed in a situation in which she will have to choose a course of action. Her primary conflict regards whether she has witnessed a violation of the ACUP by Jorge during the second round of surgeries. The issue is a complicated one that brings up many questions whose answers may not be immediately apparent from the facts presented in the case. Was Jorge in fact responsible for the loss of the sheep? Was the health of the animals before surgery an issue (as Jorge argues)? Was it a combination of Jorge's technique and the condition of the sheep that led to the eventual outcome? Faced with all these points, the reader is asked in the discussion questions to come up with some suggestions for what actions Mariel should take.

The validity of this case rests on the existence of a consensus between the reader and Mariel that there is indeed an issue to be raised about the animal care and use protocol. There is no question that a violation in an ACUP should be brought to the attention of the proper authorities; however, one may rightly ask at what point do you draw the line between a minor incident and a potential ACUP infraction? If Mariel had seen the animal care technician giving the animals a feed intended for goats and not sheep, she would undoubtedly not have been bothered to the extent that she was in this case. Since the differences in the feed type will most likely have few lasting ramifications in the long term, the problem with the feed could be resolved easily, with a note in the animal records and a word to the technicians to be more careful during feeding.

In an ideal world, it may be possible to say that either no infractions in an ACUP would occur, or, if they did, they would all be reported no matter how small. However, we and Mariel live in the real world, where issues such as this one are compounded by the fact that humans have emotions, opinions, preconceived notions and other concerns that affect how we view a scenario. While we are not aware of all the factors that could affect Mariel's course of action, we can consider how she might be affected by such things as desire to be loyal to her colleague, fear of reprisal if she were to blow the whistle on him, the consequences for her project if she were to jeopardize her relationship with Jorge, and the fear that she will be ridiculed for speaking out, given that she is only a beginning graduate student. For this case to be seen as realistic I feel justified in putting forth the notion that there are no cut and dried resolutions to this case (i.e. one might conceivably think that all that Mariel had to do about her problem was to talk to her adviser, but I feel that this is too simplistic a view).

The question then comes back to what actions should Mariel take? Mariel could choose to do nothing and ignore her concerns in the hopes that it was all an isolated incident that will not be repeated. If nothing did happen, then she will be justified. If, however, it should turn out later that she deliberately kept quiet after being witness to something that should have been reported, Mariel could find herself becoming party to the whole incident without meaning to.

Animals have died after the second round of surgery, when none died after the same procedures in the first round. The animals' deaths and the effect this will have on her project upset Mariel. Since she is convinced that she saw something unusual during surgery, Mariel is probably right in deciding that she needs to say something to someone about the whole incident.

Whom should she address first? The logical choice is Jorge, since he is the one directly involved. What happens next may depend on whether Mariel and Jorge can come to an agreement as to what happened during surgery.

Jorge denies that he is responsible for the sheep's deaths; he has come to the conclusion that the sheep were not well enough to survive the surgery because of their cancers. At this point Mariel could ask Jorge why he did not put forth this issue to the group at the time the ACUP was written. Surely it would have been an important point to bring up then. Certainly Jorge as veterinarian in charge was responsible for these types of concerns. Had the group been aware of his concerns

then, they might have hesitated to put the ACUP up for approval by the IACUC. Is Jorge telling the truth? Why did no sheep die in the first round of surgeries? Does Jorge have an explanation for the discrepancy between the first and second round of procedures?

Suppose that Jorge thinks about what Mariel has said, and then acknowledges that perhaps it was simply because he was tired and rushed during the second round that he did not follow his meticulous technique used in the first round. At this point, the two students have reached an accord, and resolution can follow. They can go and talk to Carroll together about what happened and discuss how to prevent it from happening again. Carroll may know what steps to take next, how to report to the IACUC if necessary, or bring in another surgeon, or even find some other way to lessen Jorge's load so that he is not so tired and busy. The case as it stands in this scenario is resolved in a fairly simple manner.

Consider an alternate situation, in which Jorge is adamant that he is not at fault. Mariel suspects that Jorge did not in fact follow the same techniques in the first and second rounds. She feels that it was these differences that affected the survival of the second group of sheep and not the fact that they had cancer. Here she and Jorge cannot reach a consensus, and it is her word against his. In this case Mariel will probably need to discuss the issue with Carroll alone. She will need to point out her concerns that the ACUP was not followed, and that Jorge may be jeopardizing her project by his actions. Carroll is in a better position than Mariel to take the situation in hand, having the advantage of seniority, and probably more experience with this type of situation.

In Part 3, the reader is asked to consider how the situation changes if the affected sheep do not in fact die, but appear to be exhibiting signs of distress and discomfort after surgery. While no animals have died, potential animal suffering is a very serious issue. At this point, Mariel should really defer to the attending veterinarian, who should examine the animals to see whether the cause of discomfort can be ascertained. If the veterinarian feels that the animals are exhibiting symptoms of post-operative distress within the range of what is to be expected after the major surgery they have had, then administration of analgesics is probably the first course of action. Use of analgesia is an appropriate and important part of a research protocol and at the time the ACUP was written, the drugs of choice should have been stipulated (note that in special circumstances, the IACUC could grant an exemption to a research project in which the analgesics would interfere with the outcome of the

study). After receiving the medication, the sheep should be watched carefully to see whether their condition improves. If the sheep recover, the project can probably continue, provided that the events were properly recorded. The researchers may want to address this issue and see if it can be avoided in the future. They may wish to examine matters such as their pre-operative care or surgical technique in an effort to reduce the chances of causing suffering in the animals after surgery.

If, on the other hand, some or all of the sheep do not improve after the administration of analgesics, then the research team may choose to have more diagnostics run on the animals to see whether further treatments could be administered to help the animals. If additional veterinary care fails to relieve the distress, then the team may have to consider euthanasia for the sheep. While the decision to euthanize the animals may be a troubling one, in the sense that in a research project such as this one the death of one animal can mean tremendous loss of data, it is unreasonable to keep the animals alive if they cannot at least be comfortable. Again, on occasion, certain research is exempted from this premise if it can be justified. Unless the team's ACUP was approved for such an exemption by the IACUC, then euthanasia is probably the only humane recourse left. While Mariel may attempt to weigh the issues of animal well-being versus the importance of the information the animal(s) can provide, it would be inappropriate for the final decision to be left to her. These types of decisions are left to the IACUC. It is up to the reviewers to determine what is justifiable and what is not. In reality, an ACUP would probably need to include information relevant to a situation such as the one described (i.e. what endpoints are reasonable, under what circumstances the animals would be euthanized, what means of euthanasia would be used).

A final point to ponder when faced with the euthanasia option is to consider how much useful data the animals can realistically be expected to provide the research team given that they are in discomfort. The distress is a manifestation of the animal(s) altered physiology, which could mean that any data collected from animals in this state might not be a true reflection of the condition the researchers are studying. In the long-term ignoring this point could lead to publication of inaccurate data, which could in turn have serious ramifications for future research in disease treatment and pharmaceuticals.

When Mariel has taken action leading to one of these resolutions, we can discuss some of the subsidiary issues in more detail. Take the issue of collaboration. Jorge, Mariel and Carroll are collaborators who all stand to gain from this project. All have a

responsibility to make this effort successful. How seriously should they take this responsibility? In the case presented here, it is apparent that Jorge's research can continue even in the event of the sheep's deaths since he only needs tissue samples. On the other hand, Mariel's work requires not only that the animals survive but also that the surgery be done correctly.

If Jorge truly is being negligent, then he is being a poor scientist in many ways. He is violating an ACUP as well as being a selfish collaborator who places his work and career above those of others. This is unethical conduct for someone who should be setting a positive example for his junior colleague. The final issue returns to the point that Jorge makes about the sheep being unfit to survive surgery. If this is something that he only realized after operating on the sheep, then he cannot be blamed for not mentioning it during the writing of the ACUP. However, at this point he should be making provisions for submitting a change in protocol to the IACUC. It is unacceptable to continue doing surgery in the knowledge that the animals will suffer and die as a result so that the only information the surgeries will provide is data that could be derived in other ways less harmful to the animals such as biopsies. Carroll and Mariel should support these changes, even if the project will be delayed or the scope of the research narrowed as a result. The ACUPs were written to make researchers more responsible for their actions, and should be seen not as a hindrance but an advance in scientific integrity.

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Suggested Reading

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