Jerald Silverman, DVM, Column Coordinator

Congruence between grants and protocols

The nonhuman primate (NHP) facility at Great Eastern University had an IACUC-approved protocol to supply blood and certain other tissues (e.g., lymph node biopsies) from live primates to researchers for their studies. Joan Collier, an IACUC member who also was an IACUC office staff employee, was carrying out a third-year renewal review of the NHP facility's protocol. As part of her office duties, Collier helped to assure that animal use procedures listed on research grants were approved by the IACUC on one or more of the principal investigator's protocols. Therefore, it surprised her to find that the use of the NHP facility tissue collection protocol by investigators at Great Eastern seemed to exceed the number of research grants that claimed to require the use of primate tissues. Collier did a little detective work, focusing on grants belonging to Drs. White and Green.

White's grant, which used monkeys in a surgical study, included blood transfusions using blood obtained from other monkeys of her own. However, she had recently begun using the NHP facility protocol to supply additional blood for transfusions. She did not report this to the IACUC, nor was it mentioned on her last non-competing renewal to her funding institute at the National Institutes of Health (NIH). In contrast, Green's research normally used only commercially available mice and mouse cell lines. But in the second year of his study, he realized that he needed to confirm some of his results by using primary cells derived from NHP lymph nodes. Therefore, he amended his IACUC protocol to add the use of the primate lymph node cells obtained from animals at the school's NHP facility, but he never informed his funding source (the NIH) of this change. When questioned by Collier about the use of the NHP facility animals, both White and Green indicated that they had nothing to do with the live monkeys; they simply obtained blood or lymph node tissue using the NHP facility's fee-for-service program. They never notified the NIH because they believed they were not using live monkeys.

Collier said that the monkey tissues obtained from the NHP facility were custom samples and could not be considered 'off-the-shelf' items. In her opinion, the researchers were non-compliant with their NIH grants. Do you think that White and Green were noncompliant with their grants? Should Green's addition of the lymph node tissue have been reviewed for its scientific merit? What role, if any, should the IACUC, NHP facility and Great Eastern University have in addressing the concerns of Collier?

RESPONSE

Hole in the system

Douglas A. Fitts, PhD

The procedures carried out for White by the nonhuman primate (NHP) facility were mentioned in her grant and were approved on her own protocol for the same purpose. They do not constitute a change in scope[1], and the samples were relevant to the work funded by the grant. White should have reported the approval date of the new protocol in her progress report. She should immediately report this to the National Institutes of Health (NIH) via the university's grant-concordance unit. A gray area that should be investigated by the IACUC is why she underestimated the amount of blood required for her monkeys. The IACUC should also determine whether she is now using her own blood donors as blood recipients.

Green initiated a change in scope on his grant without prior approval from NIH[1]. Collier was correct that ordering surgery to extract lymph nodes from living monkeys is not an 'off-the-shelf' service[2], and it does add work with live NHPs to the grant. The NHP facility must stop this contract, and the university should promptly report the event in detail to the Office of Laboratory Animal Welfare and the funding unit[3]. NIH will have to determine the scientific merit of the change because it was not included in the original review. NIH may require reimbursement of the fees and charges used to obtain and process the NHP cells[3].

There is a hole in the compliance system at Great Eastern University. Grant-concordance review is an institutional function[1] and may or may not be delegated to someone who also does IACUC protocol review. Collier was in a position to do both. Grant awardees who contract with the NHP facility for tissues are supposed to know that they need to report all uses of live vertebrate animals to NIH because it is written into the terms and conditions of the award. We do not know how the NHP facility staff members decide whether to supply tissues to a client, but they are not advising all recipients to check with their grant sponsors. An NIH-funded researcher such as Green should not be able to charge a new NHP study to his grant without a prior merit review by NIH, a Vertebrate Animals Section and a report of the protocol's approval date. It is easy for investigators to believe mistakenly[2] that fee-for-service organizations such as this NHP facility, a custom transgenic mouse facility or a custom antibody vendor do not need to be reported. NHP facility staff members could avoid these instances of noncompliance by providing information to prospective clients, but first they need to understand that they should do so.

How money is spent for animal research on an NIH grant is the responsibility of the

principal investigator (PI), the Institutional Official (IO) who signed the Public Health Service Assurance and the Authorized Organization Representative (AOR) who signed the grant for the institution. Federal regulations do not specify how compliance is monitored within an institution. The institution may establish a policy to review any purchase that risks noncompliance. This Great Eastern University policy may, as a condition for approval of a service protocol, direct the IACUC to require a PI to collect grant information from clients in order to facilitate compliance. However, the IO or AOR will not know that a policy is needed unless the IACUC is alert for service protocols that might cause conflicts with grants. IACUC reviewers must think about grants even if they have not seen or read them!

US Government Principle II requires an evaluation of the relevance of a procedure to human or animal health[4]. The IACUC and NHP facility staff members can not know how the samples will be used unless they ask the clients, and no samples should be supplied unless they are to be used in a relevant scientific endeavor. If the fee is to be charged to the budget of a grant, NHP facility staff members can simply check with the grant-concordance unit before supplying the tissues. Collier can inform them whether the samples were included in the funded grant (that is, were meritorious according to NIH) and whether the approval date was reported to the sponsor. The IACUC must also consider how to determine the relevance of samples destined for other institutions or for non-grant budgets (e.g., a departmental budget).

1. US National Institutes of Health. NIH Grants Policy Statement; Part II Terms and Conditions of NIH Grant Awards, Subpart A: General. (US National Institutes of Health, Bethesda, MD, 2013).
2. National Institutes of Health. *Policy on Humane Care and Use of Laboratory Animals—Frequently Asked Questions*. Does the PHS Policy apply to the production of custom antibodies or to the purchase of surgically modified animals? Question No. A.2. (US Department of Health and Human Services, Washington, DC, 2006, revised 2014).
3. Office of Laboratory Animal Welfare. Guidance Addressing the NIH Policy on Allowable Costs for Grant Activities Involving Animals when Terms and Conditions are not Upheld. Notice NOT-OD-07-044. (National Institutes of Health, Washington, DC, 26 January 2007).
4. Interagency Research Animal Committee. U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (Office of Science and Technology Policy, Washington, DC, 1985).

Fitts is Research Associate Professor (Retired) in the Department of Psychology and Office of Animal Welfare, University of Washington, Seattle, WA.

RESPONSE

Verify congruence

Shannon Reynolds, BA, CPIA, RLAT & Lea Smalls, BA, CRA

The scenario for White and Green raises several questions regarding the use of animals in their respective research. White has effectively increased the number of nonhuman primates (NHPs) used for her

A word from OLAW

In response to the questions posed in this scenario, the Office of Laboratory Animal Welfare (OLAW) offers the following clarification and guidance:

The issues raised in this scenario are matters of institutional and investigator compliance with the National Institutes of Health (NIH) Grants Policy Statement (GPS) and with the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS *Policy*). The relevant requirements are as follows:

White, the investigator who changed the source of the blood for her NIH-funded study, failed to inform the IACUC. The NIH GPS allows the investigator to make changes in the methodology and approach of the project without prior approval by NIH grants management[1]. However, the deviation from the investigator's approved protocol and the failure to track usage on the nonhuman primate (NHP) facility protocol are not compliant with the PHS *Policy*[2]. These incidents of noncompliance must be reported to OLAW[3].

The other investigator, Green, changed the animal model he was using after his grant was awarded, and his work required surgical collection of lymph nodes. This action, per the terms and conditions of the NIH GPS, is considered a change in scope and requires prior approval by the relevant Grants Management Officer of the NIH awarding component[1].

Additionally, staff members at the NHP facility providing the blood and tissues should refine their procedures to ensure adequate post-approval monitoring and tracking. Enhanced training for the research staff on the types of activities covered by the PHS *Policy* and considered research with live vertebrate animals would address the programmatic issues that these incidents have brought to light at the institution[4].

1. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
2. US National Institutes of Health. NIH Grants Policy Statement; Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General, 8. Administrative Requirements. (US National Institutes of Health, Bethesda, MD, 2013).
3. Office of Laboratory Animal Welfare. *Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals*. Notice NOT-OD-05-034. (National Institutes of Health, Washington, DC, 2005, updated 2013).
4. National Institutes of Health. *Policy on Humane Care and Use of Laboratory Animals—Frequently Asked Questions*. Applicability of the PHS Policy. (US Department of Health and Human Services, Washington, DC, 2006, revised 2014).

Patricia Brown, VMD, MS, DACLAM
Director
OLAW, OER, OD, NIH, HHS

research without notifying the IACUC, and Green has changed the scope of his research grant without notifying the funding agency. White and Green both state that they were not using live monkeys and seem to lack understanding of the regulations and the terms and conditions under which they are obligated to carry out their research.

The Animal Welfare Act definition of animal includes "any live or dead" monkey that is "being used, or is intended for use, for research"[1]. The Office of Laboratory Animal Welfare has published a similar interpretation, stating that the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* applies in cases where animals are killed "for the purpose of obtaining or using their tissues or other materials"[2]. In addition, the terms and conditions applied to National Institutes of Health (NIH) funding awards require prior notification for "all instances" of a change in research scope, which includes a change in animal model[3], and the institution "must be able to associate each grant or grants with a relevant protocol or protocols"[4].

Green has violated the terms and conditions of his grant by failing to report a change in scope to the funding agency. This is a serious issue and must be reported to the NIH promptly.

White's increased animal use is neither a change in scope nor an unapproved significant change, but it does raise other questions. If we assume that the grants of White and Green were not listed on the NHP facility blood and tissue protocol, then the IACUC should work with NHP facility staff members to ensure that blood and tissue are not provided to investigators unless their grants are associated with the NHP facility protocol. The IACUC office, or other party responsible for verifying grant-to-protocol congruence for the institution, should update its files to indicate that White and Green are obtaining materials from the NHP facility protocol.

Furthermore, to address the underlying cause of these problems, Great Eastern University should consider providing additional training or mentorship to its investigators, so that their responsibilities for informing the IACUC and the NIH of changes with their research are fully understood and acted upon.

1. Animal Welfare Act Regulations. 9 CFR.
2. National Institutes of Health. *Policy on Humane Care and Use of Laboratory Animals—Frequently Asked Questions* (US Department of Health and Human Services, Washington, DC, 2006, revised 2014).
3. US National Institutes of Health. NIH Grants Policy Statement; Part II Terms and Conditions of NIH Grant Awards, Subpart A: General. §8.1.2.5. (US National Institutes of Health, Bethesda, MD, 2013).
4. Brown, P. Grants Policy and Congruence. OLAW Online Seminar (7 June 2012). <http://grants.nih.gov/grants/olaw/120607_seminar_transcript.pdf>

Reynolds is Regulatory Compliance Specialist and Smalls is Grants Manager, Allen Institute, Seattle, WA.

RESPONSE

Documentation needed

Sonia Doss, RLATG, MEd, CPIA & April Kolstad, DVM, CPIA

There are three protocols at Great Eastern University in which compliance is in question. First, the protocol to provide blood and tissues to researchers should describe the blood collection and lymph node biopsy procedures and include the amount and frequency. Nonhuman primate (NHP) facility staff members should not have supplied these products to researchers who did not have an approved protocol for using them. The principal investigator (or designees) for the NHP facility protocol should request documentation of IACUC approval from each individual investigator requesting tissues and blood prior to supplying the products. As an assurance to Great Eastern University's IACUC, the NHP facility protocol should also include a list of the amount of blood and other tissues provided to each investigator, along with the associated IACUC protocol number and grant number, in the annual progress report. If this information had been provided and reviewed on an annual basis, Collier may have identified the discrepancy before the third-year renewal.

White is out of compliance on her protocol for obtaining blood from the NHP facility without amending her protocol to include the option of obtaining blood for transfusions from animals other than the ones housed under her protocol. She should not use any more blood products from the NHP facility until she submits an amendment and receives approval from the IACUC. Because she does have approval for using blood in transfusions under her grant (and presumably her protocol), there is no noncompliance with her National Institutes of Health (NIH) grant.

Green is in compliance with his protocol at Great Eastern University because he amended his IACUC protocol to add the use of primate lymph node cells obtained from the NHP facility; however, he may be out of compliance with his NIH-funded grant. The NIH requires notification of any change in scope for projects using NIH-funded grants. This includes applying new technology, such as changing assays from those approved to a different type of assay[1]. It seems that Green has not changed his approved assay but merely changed the method of confirming results by adding the use of non-human primate lymph node tissues obtained from the NHP facility. He should have contacted his grants management officer to determine whether the NIH institute or center that funds his work considered it a change in scope. If the grants management officer determined that it was a change in scope, Green should have requested approval of that change in scope before implementing the change[2]. If Green determined he did not have a change in scope but was merely validating his previously obtained results, then he should have provided an explanation that the institution could file with the congruency review documentation. Presumably, when Green submitted the amendment to Great Eastern University IACUC to add the use of primate lymph nodes, he provided justification for their use in validating his assays.

1. US National Institutes of Health. NIH Grants Policy Statement; Part II Terms and Conditions of NIH Grant Awards, Subpart A: General. §8.1.2.5. (US National Institutes of Health, Bethesda, MD, 2013).
2. US National Institutes of Health. Changes in Scope on NIH Grants and Cooperative Agreements. (US National Institutes of Health, Bethesda, MD, 2013). <http://www.fic.nih.gov/Grants/Pages/Scope.aspx>

Doss and Kolstad are Compliance Liaisons, Office of Animal Welfare Assurance, Duke University, Durham, NC.