

# Respect for the PI's Ultimate Responsibility

Great Eastern University (GEU) has many faculty that serve as basic research Principal Investigators (PIs) and practicing medical doctors (MDs) with extremely busy clinical hours. These PIs are committed to providing quality care to their patients and to discovering novel treatments for the medical challenges associated with their expertise. Many PIs find it difficult to manage a robust research program while caring for their patients and, consequently, hire managers to oversee the daily operations of their research programs, including program compliance.

Dr. Felelós, a prominent GEU MD who studies neurological diseases, has been asked to appear before the IACUC to discuss a serious allegation of non-compliance. Prior to this meeting, Felelós discussed the matter with his laboratory manager, Li Wang. Felelós learned that his post-doc, Dr. Abigail, knowingly permitted animals to exceed the IACUC-approved humane endpoints to gather some critical data before they were euthanized. Once Wang became aware of the incident, she and Abigail (a) reviewed the importance of compliance and protecting animal welfare, (b) discussed how Abigail could have handled the situation differently, and (c) submitted an amendment to extend the experimental endpoints.

Because the area veterinarian was already aware of the incident, Wang felt no further action was required and intended to inform Felelós at their next update meeting.

During Felelós' meeting with the IACUC, he confirmed the accuracy of the allegation and conveyed the corrective actions Wang immediately implemented. After excusing Felelós from the meeting, the IACUC deliberated and agreed that (a) PIs are always ultimately responsible for all animal activities occurring under their protocol(s) and (b) that exceeding the protocol-defined endpoints is non-compliance that compromised the welfare of multiple animals. The IACUC voted to suspend Felelós' animal activities for 3 months.

Felelós was furious when he received notification of the IACUC's decision and immediately called the IACUC Chair and subsequently communicated his concerns to the IACUC, in writing, which included:

1. What regulatory references state that the PI is ultimately responsible for all animal activities occurring under their protocol(s)?
2. To uphold the misconception that being responsible equates with being the one who is punished, GEU's IACUC is being unreasonably punitive:

- a. Wasn't I being responsible by hiring a lab manager with the responsibility of maintaining program compliance?
  - b. Isn't the goal of corrective actions to eliminate recurrence of the incident?
  - c. Aren't Wang's actions with Abigail more effective in eliminating future non-compliance than suspending my animal research (which focuses the penalty on me and doesn't provide any mitigating training or education for the person committing the non-compliance)?
3. It is my opinion that Wang should be the PI on the IACUC protocol; why doesn't GEU permit any non-faculty to be PIs?

How would you and/or your IACUC respond to Felelós' memo?

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## Compliance considerations

The Protocol Review coordinators offer the following compliance considerations:

### 1. What is a "PI" (in reference to animal activities)?

OLAW and USDA have previously commented on the definition and expectations of the role of a PI<sup>1</sup>:

- ...all persons involved in animal use are to be qualified to perform their duties and the regulation designates the research facility as being responsible for providing training and instruction.
- The PI is defined as "an employee of a research facility, or other person associated with a research facility, responsible for a proposal to conduct research and for the design and implementation of research involving animals."

- The regulations also outline the responsibilities of the PI which include but are not limited to consulting the Attending Veterinarian on painful/distressful procedures, considering alternatives to painful/distressful procedures, and providing the appropriate medications for procedures causing more than momentary or slight pain/ distress unless withholding is scientifically justified in writing.
- As a result, it is the responsibility of the IACUC to determine whether persons designated as the PI using an AWA-regulated species meet the definition and fulfill the qualifications and responsibilities as set forth by the regulations.
- The PHS Policy does not contain specific guidance on who can serve as PI for research involving animals. The Policy at IV.C.1.f states that "the IACUC shall determine that personnel conducting procedures on the species being studied

will be appropriately qualified and trained in those procedures."

- The flexibility provided by the Policy allows the institution to define the PI within the constraints that it finds acceptable.

### 2. Regarding non-compliance resolutions:

In response to a non-compliance event, regulatory agencies want to know what occurred and what action(s) are being taken to eliminate recurrence (either with the specific lab or as a programmatic concern). Federal mandates leave it up to the IACUC and institution to determine the type or nature of corrective action plan(s) (CAPs) - however, the CAP(s) should be specific to the nature of the non-compliance and targeted to the root cause.

A common complaint about IACUCs is their use of punitive measures in response to non-compliance. Frequently,

IACUCs believe that the PIs are not sufficiently committed to their oversight of animal activities and that the IACUC's punitive approach will make the PIs better

## A WORD FROM USDA AND OLAW

### Response from USDA

The Animal Welfare Regulations (AWRs) define *primary investigator* as the person “responsible for a proposal to conduct research and for the design and implementation of research involving animals<sup>1</sup>.” As the named PI, Dr. Felelós retains responsibility for implementing the research activities approved by the IACUC, regardless of his choice to delegate oversight authority. However, the research facility is ultimately responsible for ensuring compliance with the AWRs<sup>2</sup>. The IACUC, as an agent of the research facility, is required to review and approve significant changes regarding the care and use of animals in ongoing activities<sup>3</sup>, and Dr. Abigail's decision to exceed IACUC-approved humane endpoints represents a critical non-compliance<sup>4</sup>. Furthermore, the IACUC is empowered to suspend an activity that it previously approved if it determines that the activity is not being conducted in accordance with the description of that activity provided by the PI and approved by the Committee<sup>5,6</sup>. Accordingly, the IACUC's actions in this scenario are consistent with the AWRs.

### Response from OLAW

NIH and other federal agencies who abide by the PHS Policy hold the PI responsible not only for the scientific and technical aspects of a grant or contract award, but also for ensuring compliance with the PHS Policy when using live vertebrate animals<sup>7–9</sup>. Likewise, the *Guide* addresses PI responsibilities in multiple areas including humane endpoints, and occupational health and safety<sup>10</sup>. The PI retains these responsibilities even when delegating aspects of the research oversight to a team member.

Regarding responsibility for noncompliance, the PHS Policy does not define who must serve as the PI. It is acceptable for different individuals to be named on a funded award and the IACUC protocol<sup>11</sup>. In this case, the lab manager promptly took corrective measures to address the failure to adhere to the protocol, a noncompliance reportable to OLAW<sup>12</sup>. However, the delay in notifying the PI and the IACUC indicates improved communication is necessary that the IACUC must address. While the IACUC has authority to suspend an

understand their responsibility or somehow take the responsibility more seriously. However, this approach assumes that the non-compliance was committed due to

activity if indicated<sup>13</sup>, another approach is collaborative engagement with PIs to achieve compliance. This may include refresher training and allowing other qualified individuals to serve as the PI on IACUC protocols<sup>14</sup>. OLAW supports progressive corrections and escalating sanctions in response to the severity and repetition of a noncompliance. □

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a lack of oversight by the PI rather than the slew of more realistic reasons, such as the practicality of the training program, turnover of staff, and/or simple human error.

Another potential misconception is that recurrence of non-compliance (or lack thereof) is the best metric for determining effectiveness of IACUC sanctions. Thus, penalizing the PI is considered effective when the non-compliance does not recur. However, if the root cause of the non-compliance was not identified, then the effectiveness of the resolution (i.e., sanction) cannot be evaluated and institutions are left with ‘not knowing what they don't know’ (e.g., non-compliance can still occur even if the IACUC isn't informed of it).

### 3. Regarding the PI's 'Responsibility':

The PI holds responsibility and accountability for the research activities (animal and non-animal) conducted in their lab. As often occurs, PIs such as Felelós, who have demanding clinical responsibilities, hire a lab manager to oversee the daily operations of the basic science lab. In essence, hiring a lab manager fulfills the PI requirement of being responsible for their animal research activities. In effect, the PI's responsibilities are the defined job requirements of the lab manager.

In this scenario, Felelós exercised his responsibility by hiring Wang; and Wang, in turn, fulfilled her role and addressed the non-compliance that occurred. It is the opinion of the authors that the IACUC should recognize the level of responsibility taken by the PI when a lab manager is hired to oversee their animal use activities. The IACUC should consider the circumstances and cannot hold the PI as “ultimately responsible”, and not accept the PI's corrective actions (e.g., punitive actions taken against the hired lab manager) to eliminate recurrence of the non-compliance. By suspending Felelós' animal privileges, the IACUC disregarded the responsibility of the PI whilst simultaneously penalizing the PI in the name of holding him responsible. □

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# Yes, You Are Responsible

This scenario is not uncommon. In many large research labs, the Principal Investigator (PI) oversees a lab with a large number of research scientists, research staff, postdocs and graduate students. In many cases the PI is not aware of the day-to-day actions of this multitude of staff and trainees, even with a lab manager. Moreover, the oversight of the trainees (postdocs and students) may be lacking and the desire to achieve results by these individuals may override the requirement to conduct good science that incorporates animal welfare.

In this scenario, a postdoctoral fellow failed to adhere to approved endpoints in

an effort to obtain additional data. This is clearly a noncompliance and must be dealt with by the IACUC. Although it may seem a bit harsh, the IACUC is certainly within their charge to suspend animal use activities in Dr. Felelős' lab. This situation severely impacted animal welfare and is not trivial. Yes, it is true the IACUC could have focused on the postdoc and simply suspended the postdoc until additional training was complete. This scenario does not provide any history of non-compliant events from the lab that may have contributed to the IACUC's decision or if the Institutional Official (IO) was consulted before announcing the decision. Both would be

important considerations when handing down a suspension of animal research activities.

This event occurred in Dr. Felelős' lab, and he bears responsibility for the activities in his lab. This is clearly laid out in multiple regulatory documents that are noted and succinctly stated in the *Guide for the Care and Use of Laboratory Animals, 8th Edition*, "The *Guide* endorses the responsibilities of investigators as stated in the *U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (IRAC 1985; see Appendix B). These principles direct the research community to accept responsibility

## WHAT'S IN A NAME?

In the scenario presented, the GEU IACUC holds that responsibility for fidelity between procedures performed and those approved ultimately lies with the Principal Investigator (PI). In contrast, Dr. Felelős, whose surname translates from Hungarian to "responsible," does not dispute that noncompliance with the approved protocol occurred, but, rather, appears to question the existence of any regulatory basis for this assertion. In this regard, we will assume that PHS Policy, the *Guide for the Care and Use of Laboratory Animals*, and the USDA Animal Welfare Act Regulations (AWRs) are relevant to Dr. Felelős' research at GEU. While neither the PHS Policy nor the *Guide* note a responsibility of the PI for ensuring compliance of activities with approved protocols, the AWRs define a PI as someone who is "...responsible for a proposal to conduct research and for the design and implementation of research involving animals" (§ 1.1) and state that the IACUC may suspend an activity that is not being conducted in accordance with the description of that activity provided by the PI and approved by the Committee (§ 2.31)<sup>1</sup>. Of note, if the work under question was funded by PHS, the IACUC should direct Felelős to the *NIH Grants Policy Statement* which specifically states an expectation that "...the PI agrees to accept responsibility for the scientific conduct of the project..." (2.3.7.6)<sup>2</sup>. Many institutions define a responsibility for PIs to ensure compliance for work conducted under their direct and indirect supervision either in a policy or as a condition of protocol approval by the IACUC.

The particular noncompliance associated with this scenario seemingly resulted in detriment to animal welfare, as humane endpoints were exceeded. Though protocol noncompliance is not specifically defined in any of the applicable regulatory or guidance documents, the expectation that animal use activities be approved by the IACUC suggests that any excursion beyond what has been approved is generally not permissible<sup>3</sup>. Related to this, The *Guide* specifies the importance of "observation of laboratory practices and procedures and comparison with approved protocols" as an essential PAM component, a sentiment echoed by AAALAC and which strongly suggests an expectation for compliance with protocols<sup>4,5</sup>.

In this case, the PI contends that he has demonstrated proactive responsibility by hiring a lab manager and undertaking corrective actions once the noncompliance was identified; and that, against that backdrop, the sanctions applied by the IACUC are unreasonably harsh. We are unaware if prior instances of noncompliance in this laboratory were a factor in the IACUC's decision, but we will assume that a history of noncompliance for this laboratory does not exist. In that case, we agree that the IACUC may have been overzealous in its approach. However, no regulatory or guidance documents offer an algorithm for sanctions to be applied in instances of noncompliance, and IACUCs are allowed to apply sanctions at their discretion.

The overall goal of the IACUC should be to ensure compliance of activities with regulations and policies. In this regard,

the overarching goal should be to build a bridge of communication and cooperation through dialogue with investigators. If such circumstances happened at our institution, we would encourage the IACUC to reflect on the proactive efforts Felelős made to correct the situation and understand that, in a first instance of noncompliance, a less aggressive approach that does not require a 3-month cessation of work should be considered. This would help foster a culture of interactive collaboration with investigators, one that ultimately seeks to promote the synergy between good animal care and research. Such an approach might include, for example, additional, targeted training of personnel in Felelős lab to emphasize understanding of those elements that led to noncompliance in the current situation. □

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for the care and use of animals during all phases of the research effort<sup>1</sup>.” The argument that he should not be responsible for protocols submitted, and animal work conducted in his lab, rings hollow. Moreover, if the animal use protocol used at Great Eastern University is similar to the one used at virtually all other organizations, he signed the form indicating he will assume responsibility.

In response to Dr. Felelős’ memo I would invite Dr. Felelős, the Attending Veterinarian, the IO, and Dr. Felelős’ Department Head to a meeting. At the

meeting I would note there are multiple regulatory documents that require him to be ultimately responsible for animal activities in his lab. The hiring of a lab manager does not absolve him of this responsibility. We would discuss this event in detail and any other events the IACUC considered. It is possible the sanction could be modified, but most likely not.

As for effectiveness of the action, in my experience nothing gets the attention of an investigator and their lab group like suspending their ability to conduct animal research. It is for this reason I strongly

believe that the Principal Investigator must be the PI on the IACUC protocol. □

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