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Postapproval Monitoring Practices at Biomedical Research Facilities

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Federal regulations and policies require institutions to establish procedures for ongoing IACUC oversight of approved animal care and use program activities including animal procedures. To fulfill these requirements, research institutions implement postapproval monitoring (PAM) programs designed to assure compliance in animal activities. Although several references commenting on the requirement to conduct PAM are available, few publications discuss actual best practices for accomplishing PAM. Here we use information collected through a survey of large academic research institutions to identify common practices for conducting PAM reviews. Many similarities and differences exist between institutions, which may or may not influence the overall quality of an institution's PAM program.

Abbreviations: ACUP, animal care and use program; OAW, Office of Animal Welfare; PAM, postapproval monitoring

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Ongoing oversight of IACUC-approved animal activities is required by the USDA and Office of Laboratory Animal Welfare policies and laws governing the care and use of vertebrate animals in research, instruction, and testing activities.[1,14] The topic of postapproval monitoring (PAM) made its inaugural appearance in the 8th edition of the *Guide for the Care and Use of Laboratory Animals*.[10] The *Guide*, a primary governing standard, describes the benefits that an effective PAM program can have for an institution. However, neither the USDA nor Office of Laboratory Animal Welfare defines specific processes for conducting PAM. The *Guide* provides several possible strategies for conducting PAM. This flexibility allows each institution the opportunity to design and implement the PAM program that best fits its own oversight needs yet meets regulatory requirements.[1,16,20]

Most protocol noncompliances appear to stem from 'research drift' or lack of attentiveness to the IACUC-approved protocol rather than from overt disregard for regulations and policies.[3,6,12] Animal Care and Use programs (ACUP) can best develop an effective PAM process by beginning with the premise that busy staff with active and progressive research activities may experience unanticipated protocol drift. This situation means that any lab, despite best intentions, is vulnerable to noncompliance. PAM programs that are strictly compliance-focused risk impeding research groups from partnering with the IACUC with the goal of research compliance, thus potentially delaying the identification of minor noncompliances, allowing them to become significant animal welfare issues and possibly result in substantial financial cost, poor-quality research results, loss of research time, and negative publicity for the institution.[3,12] As such, one of the best ways that ACUP can defend the institution is by adopting a position of "Where (or what) are the compliance concerns?" as compared with "Are there compliance concerns?"[3] PAM programs appear to be most effective when researchers feel that they are collaborating with the PAM monitors and helping to ensure the success of their research programs and the institution's reputation. It is important that PAM monitors, who generally serve as the eyes and ears of the IACUC, forms a collaborative relationship with the researchers whom they are evaluating. They must collaborate with laboratories to capture emerging issues and resolve concerns before they become serious animal welfare or compliance concerns. An effective PAM program provides objective information that the IACUC can use to analyze, predict, and develop operational strategies, which in turn can foster ongoing program improvement. Lastly, PAM can facilitate communication and promote dissemination of ACUP policy and programmatic changes through discussions that may arise between researchers and PAM staff during the monitoring process.[3]

Researchers are commonly concerned about regulatory creep and the perception of an increasing regulatory burden.[18,19] One reason why governing standards avoid being prescriptive and have thus far empowered institutions to establish their own customized PAM programs that suit their research portfolios has been to limit unnecessary self-imposed regulatory burden by research institutions.[4,9,19,22] An institution's ability to customize the PAM program to appropriately balance regulatory burden with compliance, in combination with a strong PAM program's ability to mitigate noncompliance before it becomes a major regulatory issue, makes PAM a valuable tool for the IACUC to use in efforts to decrease self-imposed regulatory burden.

To echo a former Chair of the IACUC at the University of Pennsylvania, Dr Alan Rosenquist, "Let's regulate ourselves or someone with a '.gov' address will do it for us."[11] It seems the animal research community has agreed with this statement. Formal ACUP PAM programs began appearing as early as 1997. In 2002, there was a report on research integrity by the National Academies of Science, which specified that to optimize responsible conduct of research, institutions must continuously self-evaluate their efforts through a system of

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performance-based assessments that are initiated and implemented internally.[13] Between 2005 and 2011, the investment in PAM programs grew, with a 200% increase in the number of institutions hiring dedicated PAM staff.[8] During this time, ILAR published an entire edition of the *ILAR J* dedicated to animal use oversight, and, in 2011, the 8th edition of the *Guide* had a section dedicated to PAM.[4,10]

Although previous publications have discussed how institutions might establish a PAM program, no publication has reported how institutions with PAM programs are currently achieving set goals.[3,17,23] The goal of this project was to provide information to the animal research community regarding how academic research institutions are achieving enhanced programmatic integrity through the engagement of PAM. This information will help institutions assess their PAM programs relative to those that are being used effectively at other institutions.

Materials and Methods

A survey was used to gather ACUP demographics from NIH-funded research institutions. The survey was designed to identify information on 1) ACUP and IACUC demographics; 2) PAM program design, and 3) other details relative to institutions' ACUP. The top 100 funded research institutions from 2016 were invited to participate,[5] with 55% completing the survey. The results of the survey were anonymous, and not all of the institutions answered every question on the survey. All surveyed institutions were AAALAC-accredited, and as such, each institution's PAM program had been assessed by an external agency within the last 3-y period.

A primary goal of the current study was to identify similarities in PAM programs among the nation's top NIH-funded research institutions. The survey design afforded respondents opportunities to detail PAM program design, characteristics, and functionality.

Results

For comparison purposes, the size of an institution's ACUP was quantified according to program demographics (Table 1). The data revealed that 74% of the participating institutions managed large ACUP with more than 300 approved IACUC protocols, and 91% have more than 10 IACUC members. In addition, 76% of the responding institutions maintained a daily averaged census exceeding 10,000 cages of rodents, with all conducting studies that involve USDA covered species. For the purpose of this survey, groups reported full-time staff of the Office of Animal Welfare (OAW) and IACUC together.

There was significant variation between institutions regarding the means of IACUC protocol review (Table 2). Furthermore, there was a marked difference in the frequency of institutions using designated member review compared with full committee review between the USDA-regulated species and mice and rats, with full committee review being performed more frequently for USDA-regulated species. In addition, 81% of institutions reported using the USDA pain and distress categories for mouse and rat protocols that were not covered by the USDA.

Although the survey highlighted many variations in PAM programs among responding institutions, it also revealed several common trends. For example, 42% of the institutions had formalized their PAM programs into written policies approved by the IACUC. In addition, many institutions incorporated several traditional programmatic activities as part of or supplement to their PAM programs (Table 3). Furthermore, 59% of the reporting institutions indicated they had dedicated staff to perform PAM reviews, whereas 41% did not have a dedicated staff member for PAM or compliance monitoring. PAM results were reported directly to the full IACUC (57%), the Director of the IACUC office (26%), a designated subcommittee of the IACUC (10%), or the attending veterinarian (4%).

The frequency with which protocols underwent PAM was based on risk assessment to the institution (based on a hazard analysis or risk assessment) or was performed at a set frequency. Among the institutions with USDA-regulated species, 51% based the PAM audit frequency on a risk assessment, dependent on procedures with the protocol, whereas 36% determined PAM audit frequency independent of the procedures within the protocol. Similarly, among the institutions with mice and rats, 69% based the PAM audit frequency on a risk assessment, dependent on procedures with the protocol, whereas 18% determined PAM audit frequency independent of the procedures within the protocol. When risk assessment was used to determine the frequency of PAM activities, the factors that were reported to establish this frequency included a previous history of noncompliances; IACUC-approved procedures expected to cause more than momentary pain or distress that, for scientific reasons, could not be alleviated; procedures with potential for pain or distress but relieved by treatment; protocols requiring satellite housing locations; and protocols approved for multiple survival surgeries for both USDA-regulated species and mice and rats. When PAM was scheduled on a set frequency, 72% of institutions scheduled PAM annually for USDA-covered species and 56% of institutions scheduled PAM annually for mouse and rat protocols. In addition, 86% of respondents answered that their institution consistently achieved their institutional PAM goals for USDA-regulated species, whereas 80% routinely achieved their institutional goals for PAM of mice and rats. Only 16% of institutions regularly monitor the animal husbandry program, and 10% monitor the veterinary care program.

The activities performed during routine PAM of protocols involving USDA-regulated species were very similar to those performed during PAM of protocols involving mice and rats. Most institutions routinely included reviews of the IACUC protocol, animal medical records, procedural (surgery and anesthesia) records, and personnel training records and observation of procedures; however, many institutions did not perform all of these procedures at each audit. Approximately 1/3 of institutions reported observing a surgical procedure for all protocols that included surgery, independent of species, whereas just 8% did not include the observation of a surgical procedure. The remainder of institutions observed surgical procedures as part of the PAM audit but not in all protocols that included a surgical procedure. Other activities that were reviewed as part of PAM included the study animal condition, husbandry procedures, drug storage and documentation, animal transportation, laboratory safety, and laboratory occupational health records. Several institutions also used the PAM as an opportunity to update labs IACUC policies and review the status of ongoing projects.

When concerns or noncompliances were noted during a PAM session, IACUC used several different techniques to address them. Most institutions reported using lab member retraining (90%) as a technique to address noncompliance. When retraining was required, respondents reported that staff responsible for retraining were as follows: 22% had dedicated training staff; 19% used veterinary staff; 16% indicated the principal investigator or lab manager was responsible for retraining; and 6% used dedicated compliance staff. The remaining institutions use a combination of these personnel for retraining. In addition,

Table 1. Descriptive data of the Animal Care and Use programs participating in the survey

	<300 protocols	300–500 protocols	>500 protocols
No. of approved IACUC protocols	26%	35%	39%
	50–100 PI	100–300 PI	>300 PI
No. of principal investigators (PI)	11%	63%	26%
	≤10 members	11–20 members	>20 members
No. of IACUC members	9%	69%	22%
	0–2 employees	3–5 employees	≥6 employees
No. of full-time employees working for the IACUC or OAW	8%	57%	35%
	0 veterinarians	1–3 veterinarians	≥4 veterinarians
No. of IACUC or OAW veterinarians	48%	40%	12%
	0–2 veterinarians	3–5 veterinarians	6 or more veterinarians
No. of clinical veterinarians	27%	38%	35%
	<10,000 cages	10,000–25,000 cages	>25,000 cages
Mouse and rat censuses	24%	38%	38%
	<20 animals	20–100 animals	>100 animals
Combined census: NHP, dogs, and cats	46%	31%	23%
Other USDA-regulated species census	20%	32%	48%

Table 2. Methods of IACUC protocol review for USDA-regulated species and mice and rat protocols.

	USDA-regulated protocols	Mouse and rat protocols
Designated member review unless full committee review requested	28%	44%
Designated member review except for select categories[a]	4%	4%
Full committee review for all protocols	38%	26%
Full committee review for all category D and E protocols	6%	4%
Full committee review for all category E protocols	20%	22%
Others	4%	not applicable

[a]Exceptions to DMR for USDA-regulated species included full committee review for just NHP, surgical, or prolonged restraint protocols, and for mice and rat protocols, included multiple surgical procedures, prolonged restraint or new investigators to the institution.

most institutions referenced protocol amendment submission (95%) as a means of addressing problems; 80% of institutions reported that they had required a follow-up observational PAM visit; 73% asked the laboratory to stop performing problematic procedures; and 55% reported that they had laboratories create or modify existing laboratory Standard Operating Procedures to address the concern. Many institutions also mentioned suspending a protocol, contacting regulatory authorities, and initiating a compliance investigation when findings were substantial enough to warrant more aggressive actions. When asked whether postapproval monitors were permitted to use professional judgment and educational opportunities to bring protocols into compliance and not formally report findings to the IACUC, 57% affirmatively responded, whereas 43% responded that this option was not practiced at their institution. Furthermore, 47% of institutions reported that they tracked data from PAM annually to review comparisons over time.

A total of 62% of respondents said that they believed the majority of researchers valued their PAM program as a mechanism for researchers to remain free of noncompliances. Another 12% said they believed their researchers did not value PAM activities, and the remainder responded that they did not know the opinion of the researchers.

Discussion

The federal government requires that research institutions have a process to monitor ongoing oversight of IACUC-approved activities. None of the regulations are prescriptive in dictating how these goals are accomplished, thus leaving institutions with substantial flexibility in implementing a

Table 3. Percentage of institutions using specific monitoring procedures as part of their PAM program

	Institutions (%) reporting use of the item
Semiannual inspection or program evaluation	95%
Audits of IACUC protocols or laboratories by an IACUC member or IACUC employee or IACUC designee	87%
Congruency between grants and IACUC protocols	74%
Examination of live animals or their records while on study, independent of PAM audits	49%
Unscheduled facility inspection, independent of semiannual inspections	41%
Formal evaluation of the animal husbandry program, independent of semiannual inspections	16%
Formal evaluation of the veterinary care program, independent of semiannual inspections	10%

methodology for this oversight. One method is through a PAM program. Ideally, PAM programs should be designed collaboratively between the IACUC and the researchers, with the intention of supporting the goals of the scientific project, preventing noncompliances, and identifying noncompliances while they are minor, thereby preventing minor issues from becoming major animal welfare concerns. Through surveying a sample of the top-funded NIH institutions, we found there was substantial mechanistic heterogeneity among respondents with respect to some PAM procedures, whereas in other areas, PAM procedures were quite similar. The suggestion is that although institutions may differ greatly in structure and scope, certain PAM methods appeared to be implemented in a variety of settings.

Several findings were surprising. For example, running an effective PAM program can be an expensive undertaking, both financially and in terms of time for IACUC and research staff, and requires careful planning and thoughtful execution. However, despite the institutional investment necessary for a PAM program, only 42% of institutions reported that their IACUC formally reviewed their PAM program. Continuing IACUC review and approval of a PAM program, with support from the Institutional Official and senior institutional leadership, is one means by which the ACUP could define, or redefine, its goals and expected PAM procedures. This refinement could include the frequency of PAM visits, the components of the ACUP to be monitored, and the mechanisms by which monitoring would be accomplished.[12] In addition IACUC review and endorsement of the goals and methodologies for PAM could be used as a marketing tool to get support from the greater research community, thus helping to foster a culture of compliance campus-wide. We believe that having formal institutional and IACUC approval is a valuable buttress that encourages researcher confidence and minimizes the 'animal police' approach to compliance oversight.[15] Another benefit of having a formal IACUC review of the PAM program is that the IACUC could then be empowered to set expectations for the reporting of noncompliances by postapproval monitors.

Another surprising item was that PAM programs generally had a goal of being collaborative, benefiting the researchers as well as the institution and that 62% responded that they felt that most researchers valued the PAM process. We surmised that this view reflected the perception of a favorable collaborative process by the respondent who completed the survey. That being said, 12% of institutions reported that the majority of researchers did not value their institutions' PAM process. Clearly there is room for improvement when the research community does not appreciate that the ultimate goals of a PAM program will serve their research program. Institutions may benefit from making a greater investment in educating researchers on ways that a PAM program can benefit them directly to try to improve these perceptions.

In addition, we found it surprising that 57% of institutions allowed monitors the freedom to facilitate corrective measures with the laboratories during the PAM, with several institutions reporting that inconsequential items were corrected on site and therefore not formally reported to the IACUC. This policy was consistent with recommendations concerning effective PAM programs and the statement from the Animal Welfare Inspection Guide, which indicates that a noncritical noncompliance would not be cited on a USDA Inspection Report if the institution's own compliance monitoring made a timely discovery and if appropriate corrective actions were immediately implemented.[7,21] However, we encourage institutions to seek IACUC input to clarify what issues would be considered inconsequential compared with those that might require formal reporting.

An encouraging finding was learning that most institutions determined the frequency of PAM reviews on the basis of risk assessment (51% of institutions having USDA-regulated species; 69% of institutions having mouse and rat activities). Risk-assessment–based PAM is a progressive manner to assure effective oversight yet minimize overburden to the research community and the institution. Clarifying the various categories of risks and the frequency of PAM sessions according to perceived risks can ensure that all laboratories would be monitored with a locally defined frequency.

The community appears split on the role of veterinary and husbandry staff in the PAM process. We reviewed articles that argued veterinary and husbandry staff as partners with the PAM program, whereas other publications addressed the value of perceiving the veterinary and husbandry staffs as separate animal user groups that should be periodically monitored and held to a similar standard of oversight as research staff—especially considering that appropriate husbandry is the basis for sustainable and reliable research outcomes.[3,7] We found it surprising how few institutions reported that they performed PAM of veterinary and husbandry staff activities as described in IACUC-approved protocols or facility-approved animal care Standard Operating Procedures beyond what is required through semiannual inspections and program reviews. Specifically, 16% of institutions reported performing a formal PAM of the husbandry program, and 41% noted performing unannounced facility inspections, independent of semiannual inspections. Just 10% monitored the veterinary care program. One potential reason why PAM programs do not commonly review veterinary care programs could be because PAM monitors might not always have veterinary training or feel comfortable calling veterinary decisions into question. We believe that programs that do not include PAM of the veterinary care staff and husbandry programs may overlook critical activities under the institutional banner of 'animal care and use.' This lack of review could become an unintended distraction if the research community perceives being slighted—"why is my lab monitored when the veterinary and husbandry care staff are not?"

Although PAM of animal care programs is not the same process as typical PAM in research laboratories, it remains a viable activity with substantial value to the welfare of research animals, sustainable outcomes of research activities, and overarching program integrity. Whereas IACUC-approved protocols cover research PAM, veterinary-approved Standard Operating Procedures can be used to assess care practices under IACUC oversight expectations and federal agencies requirements. Standard operating procedures can be compared with the care procedures observed, the purpose being to ensure that the activities are being conducted as prescribed by the AV, and expected by the IACUC and the research community.[3]

In the late 1990s, when the first institutions started to formally evaluate compliance after IACUC approval, a disappointingly low level of procedural compliance was discovered. One institution reported that as much as 80% of observed activities were not fully congruent with the written documents. As institutions instituted PAM programs, several mitigating processes resulted in changes to protocols, changes in task performance, and engagement of animal users, and the percentages of compliance began to rise rapidly. Documentation of compliance improvement at an institutional level is an important milestone that the IACUC can use to monitor program progress and serves as a measurable component of program improvement and integrity. In this context, we were intrigued that only 47% of institutions reported tracking the results of the PAM program year-by-year or evaluating the causes for rises or falls in compliance indices. Considering the institutional investment involved with establishing and maintaining a PAM program, tracking the rate of compliance and identifying specific areas of noncompliance would provide helpful information regarding programmatic focus and training opportunities and could justify current and future PAM investment decisions.[12]

Another interesting finding was that during this current era of concern regarding 'regulatory burden,' there were generally few differences between the IACUC-approval mechanisms and PAM programs between USDA-regulated species and mice and rats.[18,19] As previously discussed, 81% of responding institutions used the same scoring system for potential pain/distress in mice and rats, despite the unregulated status of *Mus musculus* or *Rattus norviegicus*. We noted the practice as an encouraging sign that institutions were generally using similar ethical considerations for the welfare of mice and rats as for 'higher-order' species. We believe that most researchers accept unequivocal links between animal welfare and the quality and reliability of the scientific results and that unrelieved pain or distress (poor welfare) has consequential effects on research outcomes.

Many of the surveyed institutions employed full-time dedicated IACUC and OAW staff. Specifically, 66% of institutions employed 3 to 5 full-time employees serving in a variety of roles, including administrative support, protocol review, compliance or PAM, and as program directors or associate directors. In addition, 69% of institutions reported that PAM was performed by staff members dedicated to compliance or by general IACUC staff support personnel. Less than 20% of institutions required IACUC members or veterinary staff to perform PAM. Having dedicated PAM staff offered several potential benefits to institutions. First, it allows staff time to specialize and focus on PAM procedures and helps to maintain consistent application of institutional expectations across the program. Dedicated PAM staff also encourages a favorable culture of compliance—that PAM is a community effort, in which the researcher is an important stakeholder, at the institution. Furthermore, dedicated PAM staff may be better able to aid laboratories with process improvement and to discourage the policing approach, which could be the perception if IACUC members performed these functions. Lastly, the involvement of veterinary staff as monitors distracted veterinarians from their primary duties of animal care and could have the potential to undermine trust between researchers and veterinary staff.[3]

Several components of a PAM session were highly consistent among most institutions, but there remained some variability, specifically in the observation of more technical activities, such as surgical procedures. Most institutions considered the observation of procedures as critical to assessing a laboratory's compliance with proper techniques—either IACUC-approved or defined through policy or Standard Operating Procedures. Approximately 1/3 of the institutions observed a surgical procedure in 100% of surgical protocols, whereas only 8% of institutions did not observe any surgical procedure as part of their PAM program. As a side note, the survey may not have elicited those institutions that did not do any surgery and thus may have biased the low percentage of institutions reporting no review of any surgical activity.

A small percentage of institutions noted that they saw the PAM session as an excellent time to communicate changes in IACUC policies and evolving programmatic expectations with laboratories. Given that communication is one of the goals for an effective animal care and use program, having information flow in both directions during a PAM session could serve to enhance researchers' confidence in the ACUP as it fostered belief that the PAM program is collaborative and ultimately for their research benefit.

A total of 59% of the respondents indicated they employed at least one full-time veterinarian in the IACUC or Office of Animal Welfare. Potential benefits of having veterinarians work in this office include: 1) veterinarians are trained to be highly observant of animal condition and wellbeing; 2) veterinarians are schooled in looking for subtle changes that might be perceived less easily by other personnel; 3) veterinarians are taught good written and oral communication skills and are trained to communicate to those with varied educational backgrounds or ethnicities,[2] and 4) veterinarians have the professional foundation to be direct and concise regarding animal welfare concerns. Employing knowledgeable, credentialed research support staff, including laboratory animal veterinarians, can result in a higher quality of sustained service provided to the IACUC, the research community, and the institution.[4]

Through communicating with the leadership of many institutions over the years, we have found that, despite the differences in sizes of institutions, most are confronted with similar problems. In one regard, that might not be particularly surprising, but the remarkable finding was that the solutions were many and frequently creative. Although each of our surveyed institutions had different programs in terms of scope, the concepts discussed by all were applicable to any institution of any size. For example, the early identification of potential noncompliance or suboptimal animal welfare, as could be accomplished by a PAM, provides an excellent opportunity to educate and correct concerns before the problem affects the study or a serious animal welfare concern occurs, ultimately becoming a major costly noncompliance issue affecting fiscal resources and institutional integrity.

We believe it is important for organizations to share shortcomings regarding their PAM programs as well as successes. We should learn from each other, building on success and detouring around suboptimal practices. In addition, learning from others and sharing valuable information can be accomplished by

attending one of several animal program administration focused meetings, such as the IACUC Administrators Association's Best Practices meetings; the IACUC 101 series; and Public Responsibility in Medicine and Research conferences, to name just a few.

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