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Post Approval Monitoring of Research Protocols: A Review on Experimental Animals Perspective

R.K. Shakthi Devan[1], N Parthiban[1], R Senthil[1], Pravin Hushangabade[2]

[1]Syngene International Limited,
[2]Bristol-Myers Squibb India Pvt. Ltd.
Bangalore, India.

Corresponding author:
R.K. Shakthi Devan,
Biocon-Bristol Myers Squibb R&D Center, Biocon Park,
2 & 3 Jigani Link Road, Bommasandra Phase-IV, Bangalore - 560 099, India.
Phone: +91 80 66334245, Email: sakthi.devan@syngeneintl.com

Abstract

Post approval monitoring (PAM) is an internal process for the ongoing research activities of approved protocols adopted by the institution. The primary goals are to ensure research methodology is conducted in accordance with the approval, evaluation of animal manipulations to reduce pain and distress, assessment of surgical procedures and post-operative care, to provide timely feedback to refine procedures and understand the proficiency of individuals on specific techniques of the species involved in experiments. The best approach should be collegial and facilitative of informed observations that provide an oversight of experiments conducted by principal investigators (PI's) along with other researchers listed in the protocol. In general, institutions can efficiently monitor this PAM process through any researcher/veterinarian/ coordinator who have considerable research experience as well as involved in the protocol review process or may be part of ethical committee for effective oversight of the animal care program. The proactive approach is fostering scientific conversation with research personnel and builds relationship by adhering institutional policies on animal research which in turn creates a positive culture of compliance throughout the institution. Collectively, PAM observation is ensuring the quality, research integrity, compliance with regulations and well-being of animals that eventually provides an opportunity for identifying educational competency, training based on observation categories and enabling the systematic communication process between animal care technicians, veterinarians, investigators, ethics committee and management for better compliance and humane care and use of animals for research.

Key words: Post Approval Monitoring, Animal welfare, Research protocol, Institutional animal ethics committee, Regulatory compliance

Introduction

The post approval monitoring of research animal use is commonly oversight by group of personnel from higher administration, veterinary, scientific staff and others as appropriate (Dale, 2008). PAM is an internal process for ensuring research activities based on the approval and supporting investigator/study director if there is any deficiency on animal procedures. The Institutional Animal Ethics Committee (IAEC, hereinafter referred as ethics committee) is required to monitor research activities throughout the animal experiments and even after completion of study through periodic reports and visit to animal facilities and ensuring compliance with all regulatory requirements, guidelines, applicable rules and laws (CPCSEA, 2010). The AAALAC and CPCSEA emphasize that periodical review of protocols as well as regular facility inspection is important for all the establishments (Ingle, 2015). The IAEC is expected to play a major role for implementing PAM at institutional level independently or as part of quality assurance program based on the size of organization. The self-monitoring system at local level is considered as central focus on assuring the animal care program and investigator is responsible for overall conduct of research activities after the ethical committee approval and is accountable for compliance of research with animals thereafter (Silk et al, 2013). Moreover, PAM activities provide guidance to ensure compliance, refine procedures thereby improving the standards and well-being of animals at all phases of research. Nevertheless, post-procedural monitoring should be periodically reviewed in order to achieve the reproducibility of experimental outcomes of research protocols consistently by reducing the variability with adequately trained investigators and other skilled stakeholders of the institution (Silverman et al, 2017). Hence, the monitoring process has increasingly received attention amongst laboratory animal care and use program (Collins, 2008) that demonstrates improved

compliance by adopting the PAM activities (Vanderford, 2015). PAM is considered as an effective tool and no defined process fits for all institutional needs, therefore an ideal system should be framed by ethics committee to fulfill its regulatory requirements through the oversight of animal care and use program (Banks, 2008). The guide (NRC, 2011) described that PAM helps to ensure the well-being of animals and provides opportunities to refine research procedures, methods including continuing protocol review and laboratory inspections. Moreover, the guide emphasizes the continuing oversight of animal activities is required as per the laws, regulations and policies. To accomplish this several methods are being used to facilitate ongoing protocol assessment and regulatory compliance. Similarly, there may be several other practices that can eventually help ethics committee to promote animal welfare as well as compliance (DeHaven, 2002). However, the intensity of PAM process should be customized regardless of program size and its complexity towards supporting a culture of caring of animals and its well-being (Klein, 2007). The primary focus of this review is to assess the current levels of animal welfare compliance, identifying the needs to improve monitoring oversight by systematic implementation and good documentation practices in animal facilities.

Implementation of PAM Program by the Institution

The PAM concept can be drafted by veterinarian or researcher in consultation with ethics committee and reviewed by stakeholders to create a written document such as guideline or SOP for the institution. This can be refined over the period as and when need arises by incorporating the best practices. This transparent system is readily adaptable by any institution as this is an internal self-regulation constituted based on ethics committee as well as management. Broadly, the PAM visits may be conducted in two ways i.e. a) protocol specific observation to ensure the animal procedures are performed in accordance with approval; b) Periodical facility visit combining with protocol of selected procedures. However, the ideal practice may be to conduct visits separately with more focused purpose for better outcomes. There is a scope to discuss with investigator / ethics committee / veterinarian to revisit later apart from semiannual and/or annual review to establish a successful program. However, it is mandate that all personnel working in the laboratory should have adequate knowledge of protocol and associated study plan / guidelines / SOP to perform animal procedures with confidence. Thereafter, periodical training is necessitated to assess their proficiency in order to carry out the procedures appropriately

PAM framework and Strategy for Successful Execution

The institutions can devise a viable plan for ensuring research activities to monitor previously approved protocols through a collegial approach between animal program management and animal user groups. The effective PAM observation broadly improves institutional values by adhering compliance in their research that involves the following areas but not limited to-

a) The ethics committee should provide clear guidance and directions of PAM observation with the support of management.

b) Establish a framework as per the requirement of the institution and conduct PAM observation for priority/ high risk activities which may be evolved further to become fully functional over the years.

c) Begin the monitoring oversight of approved protocols by ensuring humane care and use of animals as well as procedures with pain and distress.

d) Identifying training needs based on the observations and providing training resources/support to researchers.

e) Creating better communication between ethics committee and research personnel; and encourage the investigators/animal care staff for self-reporting.

f) To identify any potential discrepancies and rectify them through amendment process.

g) Communicate the plans to research community if any ongoing problems including ethics committee related to facility and/or animal husbandry activities to establish a strong foundation and support the continued PAM activities.

h) Review of proper animal care equipment, facility resources and enrichment plans.

i) To attain higher quality animal care program to progress science through consistent manner by adhering institutional policies, laws and regulations.

j) To serve as a resource for scientific community and facilitate regulatory compliance to the institution.

Preparation for PAM visit and Monitoring Process

The PAM observation should be planned for a randomly or scheduled protocol preferably informed visit and/or may be clubbed with other facility visits. The designee/veterinarian/ PAM coordinator should gather information about the work pertaining to approved protocols including previous concerns, if any. In addition, it is good practice to keep necessary documents including easily accessible study documents and applicable regulatory materials on the day of visit with sufficient time to monitor and interact with researchers without any disturbance to the ongoing experiments. Generally, approved protocols and procedures may be observed at least twice in a year or more frequently for each protocol, otherwise, representative protocols can also be selected based on total numbers of protocols if multidisciplinary areas of research is conducted in the facility. A formal meeting may be planned prior to the visit as systematic approach or PAM visit may be performed directly and discussed based on observations

along with the stakeholders. Alternatively, multiple protocols also can be clubbed together for a meeting of any particular functional areas. The purpose of meeting with principal investigator / co-guides / researchers / scientific personnel / students involved in research/animal care staff is important as most of the time junior level staff are often performing animal procedures to carry out research work and required to communicate transparently if any discrepancies observed including better practices exhibited during the visit. The follow-up meeting may be scheduled at later dates to ensure the action taken based on observations or may be combined with next visit such a way to rectify and meet the animal welfare compliance.

Potential Areas of PAM observation

There is no exception because the approved procedures are required to carry out in accordance with protocols to meet the institutional as well as regulatory requirements. Hence, the following areas may be focused considering the critical activities involved in the animal research facilities.

a) Assessment of laboratory practices and procedures with respect to the approved protocols.
b) Review of anesthetic and aseptic surgical procedures including post-operative care.
c) Use of controlled substances and selection of analgesics.
d) Document verification pertaining to anesthesia and surgical and post-operative records.
e) Food and fluid restrictions including prolonged restraint.
f) Inspection of specialized equipment used for collecting research data and records.
g) Monitoring of adverse reactions or experimental end points affecting the animals.
h) Pain and distress categories and unexpected outcomes of the study.
i) Euthanasia of animals with approved methods in a humane manner and ensuring death.
j) Procedures listed in the protocol concerning animal welfare or treatment is not followed.
k) Personnel involved/procedures performed but not listed in the approved protocol.
l) Protocol related health and safety issues or expired materials if any.
m) Training of personnel in the specified procedures and their records.
n) Facilities/laboratories with earlier non-compliance issues and its recurrence, if any.

Documentation of PAM and Corrective action plans

The planned PAM observations should be reported as preliminary findings to investigators for his/her response by addressing the discrepancy or deficiencies of minor/major categories, if any. Identification of potential problems at early stage helps to facilitate timely correction such a way to refine the animal procedures. The PAM coordinator/veterinarian/ethics committee/team should facilitate resources that eventually provide adequate training for individuals to enhance their skillsets towards animal care program. A well-structured form is required to be created by the institution that can be used while performing the PAM observations (Appendix-1). However, there may be non-compliance that can be addressed to ethics committee through proper communication channel (attending veterinarian / member secretary) and documentation of specific finding(s) in the subsequent meeting by seeking expert opinion. In cases where significant observation is noted, it is required to notify the corrective action plans with time frame. If there are repeated discrepancies or unattended deficiencies, it should be discussed with management and ethics committee members along with veterinarian to facilitate the investigator to take suitable measures to close the non-compliance. The prompt communication between PAM coordinator and response of investigator with immediate corrective actions by amendments, refinement of techniques and animal procedures can control the variables that eventually minimize the risk of non-compliance and better reproducibility of data collected from animals which requires diligent follow-up and closed cooperation of the scientific community.

Conclusion

The post approval monitoring helps to ensure animal procedures are conducted as per the approval and provide an opportunity for investigators to refine procedures thereby improving the standards of research and welfare of animals. An effective PAM program is enabling the monitoring oversight of animal procedures / facilities that systematically provides periodical assurance of the research conducted and transparent documentation with corrective action plans, if any. PAM process improves communication and educational partnership between cross functional team members within the institution for a broad understanding to promote animal research and welfare. A well designed PAM program can be successful for any institution through collaborative efforts of ethics committee, institutional official, management, veterinarians, investigators and other stakeholder's responsibility to encourage this system driven process for better compliant of humane care and use of animals. Overall, the PAM process is ensuring the regulatory compliance by periodical visits in order to protect the institution and facilitating better science through well-being of animals.

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Appendix 1 - Post Approval Monitoring Compliance Check List

Section	PAM Checklist for key areas
Protocol, Personnel and Training	Do the PI and laboratory personnel have easy access to the most recent version of the approved protocol(s) including amendments.
	Do the PI and research personnel involved with procedure(s) have access to the approved standard operating procedures (SOPs) or guidelines and the recent version.
	Are the personnel performing the study listed on the protocol and adequately trained to conduct procedure(s) for which they are responsible.
	Training documentation is available either for individual or group of appropriately trained personnel to work with all relevant species and procedure(s)?
	Are the people involved in the study proficient in recognizing pain or distress in animals?
	In the event of a veterinary medical emergency or after office hours, do laboratory personnel know how to contact the veterinarian?.
Study Procedures and Animal Rooms	Does the cage card number match with the approved protocol number and any other pertinent information of the species (i.e., gender, age, numbers, date of birth or arrival, etc.)?.
	Are the animal rooms and/or laboratories clean, neat, and in good operating conditions (including sinks, drains, ceilings, working surfaces, etc.)?
	Are laboratory-housed animals kept under appropriate environmental conditions (light cycle, temperature, enrichments, group density, etc.)?.
	Are the procedures performed consistent with those approved in the protocol?.
	Are research personnel appropriately trained to perform the procedures. Steps taken to minimize or prevent the pain and distress during handling or restraining procedure?.
Anesthesia and Analgesia	Are the methods of anesthesia in compliance with the approved protocol?.
	Are anesthetized animals monitored and supported according to the approved methods in the protocol?.
	Are the animals maintained at an appropriate depth of anesthesia for the procedures performed?.
	When inhalant anesthetics are used during the procedure, the inhalants are scavenged properly?.
	Are anesthetic machines routinely serviced and calibrated?.
	Are analgesic dosages, frequency and routes of administration are adequate in accordance with SOP/ guideline?.

Surgery (Survival and Non-survival)	Survival surgeries are performed under aseptic conditions/ approved areas?. Is there a dedicated area for animal preparation and in accordance with SOP/guideline?.
	Is an appropriate heat source/thermo-controlled device used to keep the animal warm throughout the procedure?.
	Is survival surgery performed under sterile instruments, sterile gloves/mask and aseptic technique.?
	Are incisions closed appropriately and in accordance with the approved protocol or SOP (sutures, staples, and/or tissue glue)?.
	The records documenting the surgical procedure are adequate and consistent with approved protocol or SOP/guideline?.
Post-operative care	Is there an appropriate recovery area for the animals and how the animals are maintained until the recovery?.
	Are animals returned to the animal holding areas in a timely manner?.
	Post-surgical care monitoring frequency is adequate and documented?.
	Are any post-operative complications observed or reported to the veterinarian?.
	Analgesics are provided in a manner consistent with protocol and SOP/guideline?.
	Any identification system to identify the surgery animals and any special bedding materials provided during post-operative care?.
Euthanasia	The methods of euthanasia performed humanely and in accordance with the approved protocol?.
	Is death assured by performing an appropriate physical/secondary method of euthanasia when required?.
	If performing CO_2 euthanasia in the laboratory, are the procedures consistent with the AVMA 2013 guideline?
	If a physical method without anesthesia is used whether approved in the protocol and SOP/guideline.?
Necropsy	The level of anesthesia is monitored based on the protocol and steps taken to avoid distress to the animals?.
	The animals are euthanized and necropsied in the dedicated areas approved in the SOP/guideline?.
	Appropriate steps taken to prevent animal distress from experiencing through visual, auditory or olfactory from other animals undergoing euthanasia?.
	Are animal carcasses/tissues disposed appropriately by approved methods of guideline/SOP?.
Protocol Specific Requirements	Blood sampling, urine/feces sampling, collection of tissues, indwelling catheters or implants, tumors, transplanted (type/size/duration etc.)?.
Record Keeping	Adequate documentation of training (i.e., certificates, affidavits, training forms, etc.) easily available?.
	Are animals identified by protocol number and individual numbers or cage cards (ear tags, tattoos etc.)?.
	Animal care and husbandry records or log available with up-to-date?.
	Are controlled substances, anesthetic, analgesics records maintained and properly stored?.
Laboratory and Safety requirements	Are drugs, suture material, and other items used for survival procedure within the noted package expiration dates?. Whether expired drugs/materials appropriately labeled and stored?.
	Are drugs, food, or other items stored appropriately (away from detergents or other laboratory chemicals)?.
	Use of pharmaceutical grade drugs or other formulations approved by the protocol and justified in the ethics committee?.
	Are there any safety issues or other concerns that pose a threat to human or animal safety, or animal welfare?.
	Is there adequate emergency signage available in the laboratory areas?.
	Are current records of laboratory inspections by safety committee is easily available and under compliance?.
	Use of appropriate personal protective equipment (PPE's)?.

Comments/Recommendations _____

Corrective Actions (If applicable) _____