FDA INSIGHTS

Elements of a Good Animal Study

An overview of the essentials for ensuring a well-designed, FDA-acceptable animal study.

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Animal studies are often required by the FDA prior to initiation of a clinical study or the marketing of a device. Given the cost and ethical considerations of animal studies, it is particularly important to optimize study design and conduct. As such, sponsors are encouraged to work interactively with the FDA before initiation of these studies and to carefully consider the following necessary elements for a good animal study.

OVERSIGHT

Sponsors may manage their own animal facilities, or contract these services to various other entities. From the FDA's perspective, it matters little which option a sponsor selects as long as the methods and records are compliant with 21CFR, Part 58. Part 58 is not specific with respect to the details and methods that aid sponsors in selecting animals, animal contractors, or in implementing methodology that minimizes noise in animal studies because it assumes that properly trained and experienced staff is in place to do this.

The interviewing of animal research staff in addition to the review of paperwork may be helpful to ensure that the standard operating procedures are actually followed and the work product is what is required. Sponsors do well to ensure that the study they have contracted for or are managing is receiving consistent oversight.

PERSONNEL

As with clinical studies, a variety of expertise must be available to ensure proper care of subjects, conduct of the study, and interpretation of results. It is important for the facility conducting the study to have specific documented experience in the methods of animal care and experimentation that speaks to a track record with the device class intended to be evaluated. Also, it is important to have a trained veterinary pathologist, and possibly additional specialized vascular pathologists, to adequately obtain and interpret gross and histopathology of the species under study. These pathologists should be consulted early in the study design so as to ensure that tissues are harvested in such a way that they can be usefully interpreted.

Good animal studies consistently indicate that the sponsor has invested in a collaboration of specialists, such as interventionists, attending veterinarians, and one or more pathologists.

METHODS OF ACQUISITION, CARE, AND SURVEILLANCE

An animal study is generally thought to start at the baseline observation. Realistically, it starts the day the animals in the study are born because all pre-existing conditions can contribute to animal variability at necropsy. Vendors must comply with USDA requirements to maintain records on quarantine, surveillance, and preventative medicine. The sponsors should take advantage of this requirement and ask for the information that will help them with their descriptive and interpretive pathology at the end of the study.

Sponsors may also consider optimizing animal studies by acquiring specific pathogen-free (SPF) stock and by housing those animals in state-of-the-art housing systems so as to protect these animals from unnecessary contamination, improper footing, and variability in housing, including variability in temperature, ventilation, diet, and light. Beware of the SPF nametag because it can mean that only the original source herd was SPF. It is important to ask the vendor how they verify that SPF status is maintained in the present generation.

METHODS OF EXPERIMENTATION

After receipt of animals into the study facility, sponsors can divide the study into key periods:

- Quarantine, Health Assessment, and Acclimation
- Periprocedural; the period just before, during, and after an operation or deployment
- Postprocedure

Whether or not the study is conducted in a Good Laboratory Practices (GLP) certified facility, adequate monitoring of the animals' health and appropriate documentation should be demonstrated. The sponsor should also be able to demonstrate that an attempt was made to try to control the experiment and to explain potential confounders in the study summary. A veterinarian should be consulted to ensure that the protocol is designed with appropriate controls and that animal husbandry and care is optimal. This is necessary to mitigate confounders in research.

Infections and spasms are common confounders in studies of the vasculature. Sound study design may also involve the use of antispasmodics, narcotics, and antibiotics not only to control pain, but also to control injuries more likely to be exacerbated by or result from spasm. Personnel hired to participate in cardiovascular device studies should have a strong command of this information and a working knowledge of common pharmacologics used to minimize them.

Sponsors should prepare in advance to control variability from deployment and tracking devices or systems. The approach to a target site should minimize confounding by potential thrombi or emboli occurring upstream from the target deployment. If studying a hemisphere of the brain or a kidney, sponsors may wish to leave one native kidney and/or artery as a control so that any lesions in the target kidney can be compared to a native control. Likewise, the investigator may want to look carefully at the ipsilateral side of the brain to a carotid stent and compare this with the contralateral hemisphere downstream from a native carotid artery.

In addition to monitoring and surveillance, sponsors and their contractors should be certain to make the most of animals at necropsy time. Complete evaluation often requires examination of more than just the tissue where a device is implanted or deployed, especially when a vital organ such as a brain, kidney, or heart is downstream from the deployment site. It is also important to examine and document normal gross tissue observations. Documentation of normal tissues and organs helps to rule out contributing etiology when interpreting adverse pathologic findings (gross or histologic). As such, it is best to mention normal and abnormal findings as part of a systematic pathology examination. Emboli and infarctions are obviously of particular concern for intravascular devices.

When explant and section samples are part of a submission, sponsors should adequately oversee the process so that handling artifacts is minimized and should fully describe in their reports the methods used for tissue harvest, section, slice preparation, and staining. Suspect tissue not related to the implant or downstream from the implant should be adequately described and stored for further reference, if needed.

TABLE 1. CHECKLIST FOR ANIMAL STUDY OVERSIGHT

- ☐ An animal vendor that can produce health records has been located.
- ☐ The vendor has evidence of the animal pathogen status.
- ☐ The animals have been screened for detectable disease before commencing experimentation.
- ☐ The animals have been acclimated to the research facility to reduce procedural stress.
- ☐ Standard operating procedures are observed for the surveillance of infection, pain and distress, and other procedural stress.
- ☐ The animal protocol contains standard operating procedures that indicate there is documentation of the animals' daily health status and the sponsor has audited the facility to ensure that the standard operating procedures are followed.
- ☐ Operative and postoperative records exist and the sponsor has ensured that they are properly completed.
- ☐ The investigation has appropriate controls; including a contralateral normal vessel if appropriate.
- ☐ Multiple deployments have not introduced potential thrombi or emboli; either from the deployment system or via multiple passages proximal to the target vessel area.
- ☐ Animals are receiving daily observations and appropriate prophylactic medicine to reduce postprocedural complications. Records of adequate dosing exist.
- ☐ A full necropsy is performed on each study animal. Normal and abnormal tissues are described in the study report.
- ☐ Suspicious lesions are cultured and harvested for descriptive pathology.
- ☐ The sponsor has collected a reasonable representation of tissues impacted by the device at the site of deployment, and if appropriate, downstream.
- ☐ A comprehensive gross and histopathology report is prepared.
- ☐ Accompanying histophotomicrographs are prepared in color and captured on CD-Rom.

RECORDS AND REPORTS

The study report should be organized in such a way that the FDA can corroborate the study conclusions through a comprehensive review of the data, records, and reports. Most sponsors prepare a study summary and submit quality assurance statements and audit reports in addition to

organized data tables. It is also necessary to document that all animals enrolled in the study are reported in the results. Full reports for institutionally approved protocols, records and reports of actual blood work, histopathology and gross pathology, radiographic data and images of histopathology, faxitron analysis, or scanning electron images may be provided in appendices. In addition to high-quality color printed radiography and histopathology images, digital image files may be provided on CD-ROM.

SUMMARY

A well-designed animal study is paramount in aiding the FDA to evaluate whether a device is reasonably safe for use in human subjects. Voluntary standards, such as the ISO endovascular graft standard, often provide guidance in the development of animal study protocols, but generally do not address basic study conduct elements. These animal study elements have been thoroughly described elsewhere in statutes, which are continually under refinement as the community learns more about best practices. Most experts agree that good study designs result in good science because variability in experimentation is minimized and observations are maximal. This article highlights some of the complexities associated with animal study conduct. Moreover, it is understood that these studies are time consuming and expensive for sponsors to conduct. Hence, the FDA strongly encourages sponsors to speak with Center for Devices and Radiological Health experts about the design, conduct, and analysis of animal studies before embarking on these projects. In addition, information may be obtained in various regulations and standards. ■

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Suggested Reading

American College of Laboratory Animal Medicine Public Statement on Medical Records used for Research Teaching, and Testing.
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Public Health Policy on the Humane Care and Use of Laboratory Animals. http://grants.nih.gov/grants/olaw/references/phspol.htm
The Animal Welfare Act; Title 9, CFR Chapter 1, Subchapter A. http://www.aphis.usda.gov/ac/publications/AWA/AWAINDEX.HTML.
U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training. http://oacu.od.nih.gov/regs/USGovtPrncpl.htm
http://www.aclam.org/PDF/pub_med_records_2.pdf.
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