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Contracting In Vivo Research: What Are the Issues?

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As a result of increasing internal and external pressures, research institutions are using contract research organizations for the conduct of in vivo research. Many issues arise when contracting animal research, including concern regarding animal health and welfare. Each sponsor institution should develop a program for outsourced in vivo research that evaluates and ensures appropriate care and use of research animals. Each sponsoring institution should consider establishing a policy and procedure for how outsourced in vivo studies will be approved, conducted, and monitored. An approved list of contract facilities can be established on the basis of accepted standards for animal care and use. Written contracts should include confidentiality agreements, the delineation of animal ownership, and the expectation to comply with all applicable regulations and guidelines for research animal care and use. Finally, a process for communication of adverse study or animal welfare events should be established. Thorough evaluation of contract organizations will help ensure appropriate research animal care and use.

Abbreviations: AAALAC, Association for the Assessment and Accreditation of Laboratory Animal Care International; CRO, contract research organization; IACUC, Institutional Animal Care and Use Committee; USDA, United States Department of Agriculture

Research institutions, whether pharmaceutical, academic, or biotechnical, are facing increasing pressure to enhance productivity. These pressures include increased public scrutiny of in vivo research, increased federal regulations, and increasing costs to deliver new molecular entities. Therefore, with respect to in vivo research, institutions are evaluating all options for pursuing animal research. More and more often, research institutions are using contract research organizations (CROs) for in vivo research. The purpose of this article is to identify, describe, and discuss potential issues encountered when contracting research animal studies.

Issues that should be addressed in the development of an outsourced in vivo research program include development of policies and procedures for managing outsourced studies, identification and evaluation of CROs, development of a database of acceptable CROs, and identification of the level of institutional oversight necessary for contracted animal work.

Policy, process, and procedures. Sponsoring institutions should consider developing a corporate or university-wide policy for outsourced studies. Many research institutions already have policies that describe philosophy about the use of animals for internal research. These policies often cover the requirement to use the minimal number of animals, use of alternatives to animals whenever possible, avoidance of duplication of research, and the expectation to meet all regulations. Those policies should be evaluated to determine whether they apply to CROs. Most internal policies can easily be updated to refer to outsourced in vivo research as well. Institutions should not abdicate ethical and moral responsibility for research animal welfare if that research is outsourced.

Outsourced studies should be approved prior to initiation. The study approval process may include research management, veterinary or institutional animal care and use committee (IACUC) approval. Clearly research management should approve all outsourced studies to ensure appropriate alignment of contracted studies with business goals and objectives. Veterinarians can assist with and ensure appropriate study design as well as animal model selection, surgical oversight, and animal care. Internal IACUC approval may provide oversight regarding matters of ethics, among other things.

Well-defined internal processes help ensure that the approval procedure for external CROs is maintained. A key internal resource can be identified to administer study contracts and to act as the primary contact. Administrative responsibilities might include routing of study protocols for veterinary, management, and IACUC approval; initial contact of potential CROs; scheduling of appropriate internal meetings to discuss CRO bids; coordination of CRO communications; and the development of Statements of Work defining exactly what is required of the CRO, purchase orders, and legal contracts. Appropriate administration is crucial to ensure that all necessary communication and regulatory aspects of contracted work are addressed in a timely and consistent manner.

A legal "gatekeeper" should be identified to develop clear confidentiality agreements covering any trade secret information. For example, some surgical or transgenic animal models may be considered proprietary, so confidentiality of those models must be established as soon as possible. Contracts also should state clearly whether a dedicated animal study area is needed rather than multiuser study areas. Ownership of animals should be clearly defined. In addition, contracts should include assurance that the CRO will comply with all applicable federal animal welfare regulations and guidelines.[1,4,5] Notification of adverse study or animal welfare events also may be included in the text of contract.

Evaluation of CROs. Evaluation of CROs is important to ensure appropriate animal care and use and ease of study validation. Evaluation of CROs comprises 2 categories: the research program and the animal care and use program. Initial discussions of the research program may include capabilities of the technical staff (number, training, skills, experience), general

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capabilities (expertise, equipment), data collection, quality assurance programs, records, and record retention system.

Evaluation of the animal care and use program may include a discussion of many other topics (Table 1). These topics include organizational structure, regulatory status, accreditation by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC), personnel qualifications, records and recordkeeping, veterinary care and oversight, animal husbandry, animal transportation, physical plant, and security. The staff reporting structure should be available in an organizational chart. The general business mission of the CRO should be known. Sponsoring organizations should ask how the institution approaches personnel training and evaluate the program. In addition, employee training documentation should be reviewed. For each CRO, sponsoring organizations should obtain the names of personnel responsible for customer service, animal husbandry, breeding program management, surgery, lab animal medicine, accounting and quality control accounting and quality control. This information should be used to develop a primary contact list.

The regulatory status and level of institutional oversight for the animal care and use program should be evaluated. If the CRO is registered by the United States Department of Agriculture (USDA) and has an Assurance Statement approved by the Public Health Service, past USDA inspection and annual reports and the Public Health Service Assurance Statement on file with the Office of Laboratory Animal Welfare should be determined. Components of the CRO not overseen by the USDA should be evaluated particularly closely. A CRO that is not AAALAC-accredited or USDA-registered should be evaluated stringently to determine the level of institutional oversight for the animal care and use program. IACUCs must be organized appropriately and function according to relevant regulations. The sponsor can request a review of regulatory documents such as IACUC minutes and semiannual reports. Sponsors can also request a copy of the approved animal use protocol prior to the start of the study.

Appropriate veterinary care is important to both animal health and data integrity. Contracting institutions can assess the adequacy of the veterinary care program by determining whether a fulltime veterinarian is present, how health care issues are reported and addressed, the credentials of personnel providing veterinary oversight, and whether adequate health monitoring and disaster preparedness programs are in use. Sponsoring institutions should evaluate differences in animal health status between the sponsoring and CRO programs and determine whether any identified differences would affect outsourced research. Discussion of health monitoring programs should cover the frequency of testing, sentinel exposure procedures, pathogen panels submitted, and the diagnostic laboratories used. CRO practices of quarantine and acclimation should be evaluated. Because CROs may provide surgical models, evaluation of the CRO surgical program is essential, including evaluation of surgeon qualifications and turnover, the number and location of surgical facilities, and standard operating procedures. Surgical outcomes and postoperative care practices, including use of analgesia, should be reviewed. Typically, the contracting institution must supply a detailed description of desired surgical procedures, including specific information on the source, type, and make of implants used. Surgeons from both the contracting institution and the CRO are most qualified to discuss details of the procedures. If the model is proprietary, confidentiality agreements should be arranged.

To allow replication of studies, details of animal husbandry must be carefully identified and recorded. These details include the type of caging, general housing, bedding, sanitation procedures, water source, and population densities used at the CRO. The type, manufacturer, and steriliztion of feed should be evaluated, and the type and amount of bedding should be specified. Water source and provision should be evaluated including details on whether water is processed, acidified, or ultrafiltered and whether water bottles or an autowatering system is used. If water pH is less than 2.5, then animals may not drink sufficiently.[2,3] If water at the CRO contains *Pseudomonas aeruginosa*, a common contaminant, health problems in rodents, especially immunocompromised animals may occur. The use of an environmental enrichment program, the type of environmental enrichment, and whether the program will affect study results should be established. If appropriate for the study, group housing and provision of nesting material and other manipulanda can be specified.

If the sponsor contracts breeding programs, several additional areas should be evaluated. The program for maintenance and monitoring of genetic integrity must be discussed. Evaluation should include the recordkeeping and reporting systems used for tracking animals. The general breeding program and production method for stocks and strains should be evaluated. Ensuring appropriate breeding programs is important to ensure lack of genetic drift and repeatability of animal models.

The delivery system or animal transportation process should be evaluated, including use of a third-party transporter and the number of stops made. These questions are central to biosecurity, appropriate animal care, prevention of cross-contamination, and reduction of shipping stress.

The physical plant and vivarium security must be critically evaluated. Facility structure; animal room finishes; heating, ventilation, and cooling systems; environmental monitoring; water supply; and lighting should be described. The *Guide For the Care and Use of Laboratory Animals* can be used as an outline and reference for this information.[4] Topics of interest include surfaces, air exchange, air balance, power backup systems and alarms, and an adequate pest control program. Some studies are disrupted by disturbances, requiring discussion of structural features designed to reduce noise and vibration. Site security systems should be evaluated in terms of access control, perimeter fencing, video surveillance capability, communication with local police units, and identification of animals and studies. Histories of failure in air flow, power, water, and security systems should be assessed, as these can all have catastrophic effects on research.

Database. A list of all ongoing outsourced activities and report reviews should be maintained. A centralized database can be developed to identify approved CROs, track ongoing outsourced activities, and identify CRO areas of expertise.

Issues to address after CRO selection. Many issues may arise during the development of an outsourcing program and during or after CRO selection. One problem may be the development of detailed study protocols. If study protocols lack detail, CROs will ask many questions, and study implementation will be delayed. Developing general study protocol templates may assist investigators.

Another problem might be harmonization of veterinary care, surgical, and animal husbandry procedures between the CRO and sponsoring institution. The need for harmonization of caging, bedding, water and other factors may be crucial to study success and cannot be overemphasized, especially with respect to animal husbandry.

Pilot or parallel studies may be necessary to ensure quality of

Table 1. Assessment topics

Organizational structure
- Obtain a general overview of the company's organization, mission, and strategy.
- List the names of personnel who are responsible for customer service, animal husbandry, building maintenance, breeding programs, transportation, laboratory animal medicine, quality control, sales, accounting, and other important areas.
- Review the roles and responsibilities of the IACUC.

Policies, accreditation, and regulatory status
- Obtain copies of the CRO's IACUC animal care and use policies and procedures.
- Obtain copies of relevant accreditations—accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International is preferred.
- Confirm whether organization is compliant with Good Laboratory Practices criteria.
- Obtain copies of current site visit and inspection reports from AAALAC, USDA, and any other agencies or ministries that regulate in vivo research.

Staff qualifications and training
- Obtain job descriptions and training requirements for personnel who have direct responsibility for the production, care, transportation, and evaluation of animals.
- Review the supervisory structure for personnel with animal-related responsibilities.
- Review the training, experience, and qualifications of personnel who administer test article, collect samples, and perform observations of, surgery, or other procedures related to animal experimentation.

Animals and animal husbandry practices
- Review the following:
  - Species and source of animals
  - Source and type of feed
  - Type of caging
  - Bedding material(s)
  - Daily care activities and normal sanitation practices
  - Waste disposal practices

Shipping and transportation (applies to animal suppliers)
- Review packing procedures, transportation routes, delivery schedules, and freight vehicles.
- Review the control processes used to maintain the safety of animals during transport.

Veterinary care
- List the professional staff responsible for preventive medicine policies and procedures.
- Review the program for establishing and maintaining disease-free barriers.
- Review the quality assurance program for monitoring animal health status.
- List the disease outbreaks that have occurred during the past 5 y.
- Review the standards and mechanisms for removal of animals from studies when appropriate and humane euthanasia is necessary.

Breeding and genetics (if applicable)
- List the primary source of animal stocks and strains used in studies.
- Review the program for maintenance and monitoring of genetic integrity.
- Review the breeding program and production methods for stocks and strains.

Notifications of animal illness and disease outbreaks
- Review the process for notifying the sponsoring organization of animal illness and disease outbreaks.
- Review the process for communicating information about animal illness.

Incident reporting
- Review the process for reporting to study sponsors any:
  - incidents involving the care and welfare of research animals
  - incidents involving facilities infiltration
  - attempts to disrupt studies
  - unusual events that might impact the integrity of a given study

Recordkeeping systems
- Review the recordkeeping systems for orders, breeding, veterinary care, facility maintenance, shipping, training, and so forth.

Physical facilities
- List the locations of each production facility or barrier with the species and strain produced at each location.
- Describe estimates of typical populations at each location.
- For each facility, review the physical structure, square footage, animal room finishes, heating ventilation and cooling system, environmental monitoring, water supply, and lighting.
- Review vermin control and monitoring procedures.
- Review fire protection and security procedures.
- Review procedures and structure designed to reduce noise.

Security
- Review perimeter security, including fencing, guards, and surveillance cameras.
- List the access points to the facility.
- Review after-hours vulnerability, such as any additional guards, lighting, and so forth.
- Review policies and procedures for visitors and delivery vehicles.
- Review screening procedures for hiring personnel.
- Review procedures for securing information, including file storage and document disposal.
- Review security of outgoing deliveries, including confidentiality and vehicle security en route.

data. Therefore, receiving data, evaluating results, and confirming acceptability of data is necessary before fully outsourcing some types of research. Good pilot data will increase acceptance of outsourcing, as will providing a mechanism for sponsor visits to CROs to monitor and evaluate procedures, data collection, and results. Sponsor visits to specifically evaluate animal care and use also may be necessary. Communication between key personnel at CROs and sponsoring institutions is essential to success of any outsourced project.

Outsourcing animal research may require that the sponsor provide certain "ethical" information, mostly related to the "3Rs." CROs with functional IACUCs may question the use of animals, species used, number of animals requested, assurance of nonduplication of efforts, and the search for alternatives particularly if "USDA-covered" animals are being used.

Another possible issue is the ability of the CRO to perform studies involving hazardous or potentially hazardous materials. Not all CROs can conduct studies requiring Animal Biosafety Level 2 or 3 conditions. Evaluation of the CRO occupational health and safety program may be necessary, including the education of appropriate employees regarding potential hazards and the program for hazard identification and risk assessment.

The reporting of adverse events (either study- or animal welfare-related) should be addressed so that the CRO fully understands what must be disclosed to the sponsor. For example, a CRO may not consider an outbreak of mouse parvovirus as a reportable study or welfare event, but the sponsor may want that information disclosed. Disclosure timelines should be developed. The term "adverse event" should be defined and agreed on before beginning the study. Terms for addressing noncompliance should be set forth in the contract as a legal requirement. Conditions and timelines for issue resolution or contract termination typically are stated in every contract. Finally, the sponsoring institution should consider what is required for study monitoring and who will perform that function once studies are outsourced and underway.

Conclusions. Each sponsor institution should develop a program for outsourced in vivo research that evaluates and ensures appropriate research animal care and use. In addition, each sponsoring institution should establish a policy and procedure for how outsourced in vivo studies will be approved, conducted, and monitored. An approved list of CROs should be established on the basis of accepted standards for animal care and use. Written contracts should include confidentiality agreements, the delineation of animal ownership, and the expectation to comply with all applicable regulations and guidelines for research animal care and use. Finally, a process for communication of adverse study and animal welfare events should be established. Appropriate evaluation of CROs will satisfy questions concerning sponsor responsibility for appropriate research animal care and use.

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