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Review Article



# Animal Welfare Standards and International Collaborations

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## Abstract

Globalization of the biomedical research enterprise is occurring at an accelerating pace. Increasingly, scientific collaborations and contracts cross national borders. Assurance that the caliber of animal research and animal welfare are consistent among countries and that such animal use is done in a humane and conscientious manner is of significant concern to the scientific community, the general public, and other stakeholders. Bridging these international collaborations is a clear scientific imperative for statistical validity of the data and reproducibility of results to ensure the animal use is both meaningful and impactful. One way to mitigate the potential confounding effects that the welfare of the animals may have on the research data is to harmonize animal care and use practices and procedures worldwide. By harmonizing the care and use of animals, using high standards that are internationally accepted, research animal welfare and high-quality science will be achieved.

**Key words:** animal welfare; collaborations; culture of care

## The Landscape of International Collaborations

More than a decade ago, Dr Alan Leshner, while serving as Chief Executive Officer of the American Association for the Advancement of Science, stated that "The scientific enterprise has become highly collaborative both within and across countries. These trends present great opportunities and increasing obligations for the scientific community…."[1] In the intervening years, the use of animals in research, testing, and education has increasingly become a global enterprise, illustrated in part by the number and scope of international research collaborations and scientific meetings as well as the number of journals publishing articles from the international scientific community. For example, across the fields of science and engineering, an analysis of the number of publications authored by multiple international institutional contributors increased from 16.7% to 21.7% in the decade ranging from 2006 to 2016; in contrast, single-institution authorship declined.[2] The authors of this report conclude that the increase in international collaborations reflects typical cross-country relationships between research laboratories, but also new scientific relationships emerging with developing countries that have expanded their capabilities. Worldwide, investment in research and development (R&D) has continued to increase. Most R&D expenditure occurs in North America, Europe, and East/Southeast and South Asia, with the latter regions accounting for 40% of R&D expenditures in 2015 (the most recent year for which numbers are currently available) compared with 28% in North America and 22% in Europe. Signaling the importance of Asia to research collaborations is the rising number of publications from scientists in China, outstripping the United States and second only to the European Union (EU).[2] Evidence that international collaborations will continue to be a fundamental aspect of the research enterprise is illustrated by the fact that the number of doctoral degrees conferred in China has risen dramatically (from 8000 in 2000 to 34,000 in 2014), while only modest increases in graduates with doctoral degrees in science and engineering have occurred in the United States, the EU, and South Korea. While the United States graduated the most doctoral students of any single country, more than one-third of those (37%)

were earned by temporary visa holders. Given the international essence of research today, the need for assurance that the caliber of animal research and research animal welfare are consistent around the globe, and that such animal use is done in a humane and conscientious manner, is a topic of significant interest to the scientific community, the general public, and other key stakeholders.

Harmonizing international interactions is a clear scientific imperative for reproducibility of results and statistical validity of data. One possible source of scientific variation is related to the level of animal welfare of the experimental subjects. However, the concept of "animal welfare" is often defined through the lens of cultural differences, shaped by economics, religious values, and collective experience. Therefore, the religious and cultural context of the country where animal research is performed may profoundly influence animal treatment. Traditions of Confucianism, Taoism, Jainism, Hinduism, and Buddhism variably speak to a relationship between human beings and nonhuman animals. Some reflect the philosophy that humans are superior to other animals and view animals as a source of food, labor, and utility. In such a perspective, a person treats an animal with kindness "not because of their inherent value but as a reflection of one's own refinement as a human being."[3] Other schools of thought, particularly those that emphasize reincarnation, place value on animals as a component of the human-animal continuum.[3] According to the Islam faith, Mohammed said, "It behooves you to treat the animals gently" (Hadith Muslim, 4:2593, see Kemmerer's discussion of religion and animals[4]). Christian-based religions generally refer to human stewardship of animals, and the Torah emphasizes compassion for animals, illustrated by the prohibition to cause pain to animals in the Talmud (*tzaar ba'alei chaim*). Thus, as the status of animals varies with religious views, so too does the level of welfare afforded them. As Fraser noted, "…'welfare' and roughly similar terms such as 'well-being' and 'quality of life,' are rather nebulous concepts….It is hard enough to agree on how to define quality of life for human beings, let alone for laboratory mice."[5] This variability in perceptions of animal welfare demand due consideration when international collaborations are initiated. In such collaborations, a clear consensus of animal welfare must be defined that frames all activities with those animals.

## Factors Driving International Research Collaborations

### Expertise and Other Human Resources

A significant driver of international collaborations is access to people with different knowledge, experience, and skills. In evaluating research collaborations that cross national borders, the National Science Foundation suggests that these interactions "indicate researchers' growing capacity to address complex problems by drawing on diverse skills and perspectives."[2] Intellectual assets and scientific expertise are spread across the globe, and the World Health Organization has recommended moving away from "silos" in health care provision.[6] To facilitate this, in 2017, the World Health Organization launched the Global Observatory on Health Research and Development (referred to as "the Observatory"), which will support "coordinated actions on health R&D." One function of the Observatory is the consolidation, monitoring, and analysis of information pertinent to the health R&D needs of developing countries. A goal of this activity is the development of and ready access to vaccines and medicines for developing countries in addition to improving research capabilities in these countries. This goal can only be met through international efforts, including international research collaborations.

Similarly, the One Health Initiative is designed to "forge co-equal, all inclusive collaborations" across disciplines and around the world (http://www.onehealthinitiative.com/index.php). This is achieved, in part, through "joint efforts in the development and evaluation of new diagnostic methods, medicines and vaccines for the prevention and control of diseases across species" (http://www.onehealthinitiative.com/mission.php). The One Health initiative fosters intellectual relationships globally to improve human, animal, and environmental health. The problems being addressed through this initiative are profound, requiring diverse expertise and a transdisciplinary approach. The optimum way to ensure the spectrum of requisite knowledge is available to address these complex issues is through the development of teams of experts from around the globe. Articles published in the *One Health* journal demonstrate both the wide range of subjects being studied as well as the positive global impact of a One Health perspective. There is also evidence that a One Health approach to addressing a public health issue can lead to greater resource efficiency and cost savings,[7] community engagement in practices that promote good health,[8] and more effective monitoring for emerging infectious diseases.[9]

### Specific Animal Types

For over a century, international scientific research collaborations have been driven by a need to access a specific animal model with limited geographic availability (rinderpest outbreaks in cattle represent one important example[10]). In many instances, certain animals or models may be naturally available only in specific geographic regions or ecosystems, for example, field research on wild arboreal primates in rain forests or studies on exotic vector-borne diseases of ruminants. Because of distances involved between the primary research facility and animal site, access to local infrastructure and equipment as well as opportunities to make significant research advances are often augmented by partnering with local researchers.[11] These collaborations require distinct consideration of responsibilities for animal use, particularly when there is an imbalance between economic development between collaborating institutions and differences exist in regional or national animal welfare legislation. In most cases, initiating investigators are required to obtain animal project approval from their own institutional animal ethics committee in addition to any permits and licenses required to conduct research in another country or region. Whenever possible, animal ethics committee approval should also be sought from the local collaborating institution to ensure transparency of research objectives and mutual recognition of 3Rs approaches to research animal use and to comply with funding agency requirements. When wildlife studies are being conducted, foreign researchers have an additional ethical responsibility to consider the anthropogenic and other impacts of the work on the well-being of the species of interest as well as its biome.[12–14] Even purely observational field studies can alter animal behavior, create increased risks for predation and poaching through habituation and alter fragile ecosystems.[15,16]

More recent trends in geographic research collaborations have arisen due to difficulties in accessing certain species, such as primates, in some countries or regions, because of animal

protectionist pressures, high regulatory hurdles, and declining public support for biomedical research in Western countries.[17,18] In particular, restrictions in airline transport of primates from parts of Asia to Europe and North America have led to a dramatic increase in international collaborations to access research monkeys as well as scientific expertise, particularly in China.[19–22] Although some researchers may have initially perceived that these research collaborations would be more cost effective, because of rising economic standards in China, development of national standards for research animal welfare, and a desire to ensure that animals are maintained and research is conducted according to high ethical standards, for example, in AAALAC International-accredited facilities, differences in costs for conducting research in China vs Western Europe or North America are increasingly nominal.[19,22]

### Equipment or Facility Space Resources

Although the amount of available research funding is shrinking, the need for more sophisticated—and costly—equipment in laboratories is increasing.[23] One approach that has proved to be successful in making this equipment more accessible is through the development of core facilities or laboratories. The laboratories typically serve a large number of scientists within, and external to, the institution. Today, the research programs at many academic institutions include core facilities where services (eg, technical expertise), resources (eg, equipment), and space are shared among scientists at the institution. Examples of core facilities include flow cytometry, metabolomics, epigenetics, high-throughput, electron microscopy, and bioinformatics cores, to name just a few. Not only is there a cost savings to individual researchers, as they do not have to buy the equipment, maintain it, and train staff to use it, but these cores promote intellectual exchange between scientists and foster collaborative work. In addition, such cores recognize that a single scientist can no longer be expert in the wide diversity of equipment and technology available today. Instead, the core facilities provide this technical expertise and often consult in the planning of those aspects of the project that involve the technology.

The concept of resource sharing on a user-fee basis was taken to a larger scale by the Core for Life (www.coreforlife.eu), an "alliance" among 6 institutions that have core facilities, with an objective of minimizing overlap in investments in equipment and sharing technologies.[24] The audience of potential researchers that can be assisted by this consortium is concomitantly enlarged, as is the diversity of research resources and services provided. Such facilities are "meeting points for scientists from different disciplines and they foster exchange and integration of expertise."[24] These interactions not only enhance the institution's position in competing for external funding, but the multidisciplinary cooperations further accelerate the pace of science.[25]

## Risks and Benefits of International Collaborations

Because researchers engage in collaborations across country borders, it is important that institutions stay informed about standards in other countries. Standards of ethical oversight and care of research animals vary considerably around the world. An institution's reputation may be put at risk if a collaboration with a research laboratory located in a country with minimal standards results in harms to animals that would not be acceptable at the institution. The ethical consequences of a situation where animals are managed in unacceptable ways at the collaborating site are significant. A culture of care, conscience, and responsibility must be considered the operating norm for research institutions.[26] In this institutional culture, actions and decisions are predicated on ethics, and all individuals at the institution take responsibility for ensuring quality animal welfare. In so doing, research reproducibility and validity are optimized and stakeholder (eg, institutional employees, funding agencies, the general public, others in the scientific community, the patient population) expectations are met. It is critical that this culture of care, conscience, and responsibility extend to collaborating institutions. Without this, the institutional culture is flawed if it does not extend to international engagement with contractors or collaborators.

Intrinsic to a culture of care that crosses national borders is an attitude at all levels of the organization of doing the right thing for the right reason. There must be a value system that engenders trust in the various stakeholders. As the 2012 International Guiding Principles for Biomedical Research Involving Animals state, "The use of animals for scientific and/or educational purposes is a privilege that carries with it moral obligations and responsibilities for institutions and individuals to ensure the welfare of these animals to the greatest extent possible."[27] The institution must create an environment for synergy that promotes animal welfare among those who conduct the research and those that provide care for the research animals, both within the institution and with collaborating institutions.

When it is assured that the collaborating institution shares the same level of care and standards, both the science and animal welfare are advanced. The transfer of knowledge, experience, and expertise as well as the building of relationships between institutions and countries are facilitated, and even countries' economic engines can be driven by such cooperative arrangements.[11] These collaborations allow institutions to benchmark their animal care and use program against others around the world. In turn, benchmarking fosters the development of plans for the institution to adopt best practices and to further enhance its culture of care.

## Why Animal Welfare Policy Differences Matter

### Information That Should Be Sought From the Collaborator

Effective forging of international research collaborations involving animals requires developing mutual trust and respect between partners.[11] In addition to obtaining information about the experience and competence of a potential international collaborator for the portions of the project that they may be involved with, it is critical to determine that both parties have similar views respecting research animal welfare and that high standards of ethical research conduct will be maintained. This is essential for ensuring reproducible research and for the future ability to publish research findings. Mere lip service to one partner's ideals in this regard will not produce a sustainable partnership and may lead to early frustration. There also has to be a clear discussion of applicable standards of care that will be used as well as a detailed assessment of the animal holding and research facilities, an assessment of the availability of competent veterinary care, including medicines and other pharmaceuticals for treating disease or providing anesthesia and analgesia, a discussion of acceptable techniques, including animal endpoints and methods

for animal disposition, characterization of the specific pathogen free status of the research animals, and appropriate husbandry and research personnel training. A review of freely available research planning and conduct guidance documents, such as the Prepare and ARRIVE guidelines, may be needed to ensure consistency in approach between collaborators and an output of high-quality data.[28,29] Insufficient attention to animal welfare considerations in the collaborative research program may preclude later publication of findings.

## Ensuring Animal Welfare Standards Are Maintained

### *Whose Standards?*

When considering how to ensure animal welfare standards meet expectations at the collaborator's institution, a first step is to understand the perspective of research animal welfare both in the country where the collaborating institution is located and at the specific partnering institution. Thus, familiarity with the country's animal welfare regulatory framework is a good starting point for learning how research animal welfare is assured at the collaborating institution. Layered on the country's regulatory framework may be additional institutional policies, guidelines, and standard operating procedures implemented by the collaborator that further specify how research animals are cared for and used. Perceptions of animal welfare have both objective and subjective elements, so establishing clear criteria and mutual agreement on how research animal welfare will be maintained is essential. Potential impediments to achieving the host institution's standard of research animal welfare can include cultural views, the nuances of language, the availability of medications and supplies for the provision of veterinary medical care and good husbandry, as well as the skills and experience of personnel at the collaborating institution. Table 1 provides a list of some potential differences in animal care programs across countries.

### *Implementing a Higher Standard in the Collaborator's Program*

After agreeing on the standard of welfare for the research animals, it is critical to ensure a high level of animal care and welfare is maintained by the collaborating institution. Existing mechanisms of oversight—both internal (eg, an Ethics Review Committee, Institutional Animal Care and Use Committee, etc.) and external processes, third-party review programs (eg, government agencies, accrediting bodies) must first be determined and the details of both fully understood. Each institution should assess the systems of oversight at the collaborating institution to determine their adequacy and to confirm that the regulations and other standards are implemented and effective. If the collaborator's systems are deemed inadequate, the institution may determine it is necessary to conduct its own periodic audits. Alternatively, the institution may consider requesting copies of reports from the collaborator to provide both internal and external oversight reviews/inspections that have bearing on the animals used in the collaboration. Regardless of the model, of primary importance is the transposition of regulatory requirements, institutional policy, scientific knowledge, and ethical values into sensitivity to research animal welfare and actions that promote welfare "on the ground." To achieve this entails instilling responsibility for animal welfare through both a top-down and bottom-up commitment and engagement of personnel at the partnering institution.

**Table 1** Potential Differences in Animal Care Programs Across Countries

- How animals are obtained
- How animals are transported
- Baseline health status of the research animals
- Physical plant design and maintenance, and its suitability for the animal species and type of work being done
- Provision of adequate veterinary care
- Appropriately qualified staff
- Provision of appropriate care for the animals to include nutritious food and potable water, primary enclosure, light, temperature, humidity, enrichment, etc.
- Assurance of an ethical review of the proposed work and appropriate ongoing oversight of the animal program
- Protection of the personnel involved in the animal program
- And others

An assessment of the training offered to participating personnel provides insight into the commitment of the collaborating institution to the quality of its research output. Programs of continuing education or continuing professional development are key to ensuring that individuals at the collaborating institution remain current with international, professionally accepted standards. Assurance of project-specific training and competency applies to multiple personnel at the collaborating institution, including the internal oversight body (eg, the IACUC), the scientific staff, and animal care program staff, among others.

It may be determined that although the collaborating institution does not yet meet the expected level of research animal welfare, the collaboration is sufficiently important to warrant an investment in supporting the collaborator in meeting the necessary standards of care and use. The 3Rs framework of replacement, refinement, and reduction can be used to guide program enhancements that promote research animal welfare.[30] Some countries have either adopted the 3Rs in their regulatory environment or have requirements that include key elements of the 3Rs, such as the consideration of alternatives to the use of animals, using the minimum number of animals necessary to achieve the scientific goals, and minimizing pain and/or distress.[31] Thus, an institution considering a collaboration should review the potential collaborator's obligations under law to apply the principals of replacement, refinement, and reduction. If the country has no law that specifically references the 3Rs, a next step would be to determine if the country where the potential collaborator is located is a member of the World Organisation for Animal Health (OIE). The OIE issued standards for the "Use of Animals in Research and Education" in Chapter 7.8 of its Terrestrial Animal Health Code.[32] The OIE is recognized as a reference organization by the World Trade Organization and has a total of 181 member countries that span the globe. As members of the OIE, these countries commit to incorporating the OIE standards in their regulatory framework or otherwise conforming with OIE standards. The chapter in the Terrestrial Animal Health Code pertaining to the use of animals in research, testing, and education stipulates that oversight of the animal program ensures the implementation of the 3Rs, typically by including consideration of the 3Rs during project proposal review. The inclusion of the 3Rs in the 181 member countries' regulatory frameworks provides practical leverage to their implementation where national regulations do not specify use of the 3Rs.

Similarly, the "International Guiding Principles for Biomedical Research Involving Animals" issued by the Council for International Organizations of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS) state (principle III)[27]:

"Animals should be used only when necessary and only when their use is scientifically and ethically justified. The principles of the 3Rs—Replacement, Reduction and Refinement—should be incorporated into the design and conduct of scientific and/or educational activities that involve animals. Scientifically sound results and avoidance of unnecessary duplication of animal-based activities are achieved through study and understanding of the scientific literature and proper experimental design. When no alternative methods, such as mathematical models, computer simulation, in vitro biologic systems, or other nonanimal (adjunct) approaches, are available to replace the use of live animals, the minimum number of animals should be used to achieve the scientific or educational goals. Cost and convenience must not take precedence over these principles."

Through its scientific membership, CIOMS is representative of a substantial proportion of the biomedical research community. As of this date, the membership of CIOMS includes 41 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils. ICLAS also has an extensive international influence, manifest by its aim to promote and coordinate the development of laboratory animal science throughout the world, especially in developing countries. Therefore, the influence of the Guiding Principles, particularly those elements related to the 3Rs, has similar potential global scope and effect.

In addition, the European Federation of Pharmaceutical Industries and Associations has also fostered wide-scale adoption of the 3Rs through its membership of 33 national associations and 40 pharmaceutical companies.[33] Due to their global distribution, these associations and companies contribute to government discussions about implementing the 3Rs in new regions around the world, provide training in 3Rs practices, and serve as a role model for their implementation. Several companies have also developed specific positions dedicated to promoting the 3Rs company-wide which can be "administrative, strategic or scientific."[34] This liaison position serves multiple functions, including communicating, training, and implementing 3Rs practices and philosophies. Clearly, the influence of both individuals whose job is focused on the 3Rs as well as international organizations can be harnessed to ensure research animal welfare is assured at collaborating institutions.

#### *Monitoring Animal Welfare Remotely*

In those circumstances where standards of research animal welfare differ between an institution and its collaborator, it can be a challenge to ensure that the agreed-upon standards of welfare are sustained and do not weaken over time. The question faced by the institution, then, is how to ensure there is no reduction in research animal welfare that is unrelated to experimental outcomes. While on-site audits may be conducted, typically these occur at a periodicity of several months or more. Supplemental monitoring of animal welfare can be achieved through the use of technology and having in place a memorandum of agreement that includes information sharing. For example, an institutional representative may be able to participate via conference calls, webinar technology, or video conferencing in relevant portions of ethical review committee meetings where discussion of the protocol, program review/facility inspection (if applicable), and other business is conducted. As noted previously, copies of reports of external oversight bodies, as well as minutes of internal ethical review committee meetings, policies (eg, for humane end points, harm-benefit analysis, etc.), and inspections can be required through the memorandum of agreement. Other program documents may be requested, such as personnel training records, physical plant reports (e.g., HVAC performance), veterinary medical records of specific animals, the disaster response plan, experimental records relevant to animal health and welfare (eg, photographs or videos depicting animal condition, surgical records), and others that illustrate program operations, specifically with reference to animal welfare.

#### *Determining That a Collaboration Cannot Be Sustained*

Circumstances may arise when an institution determines that the risk of continuing a collaboration outweighs the benefits derived. Factors that influence this determination include repetitive poor reports resulting from on-site audits and ongoing reports from the remote monitoring system that demonstrate unforeseen obstacles to implementing the 3Rs, a culture of care, and other benchmarks that indicate a program is committed to ensuring high quality animal welfare. As a result, it may become evident that practices and procedures that were successfully put in place initially to ensure animal welfare have become unsustainable or have drifted substantially from expectations and there is a lack of support from or ability of the collaborator to restore them. Such a circumstance can occur when turnover of key personnel has occurred; funding, or the availability of other resources, has declined; transparency from the collaborating institution has diminished due to a change in the political (local or national) climate; lines of communication have been interrupted; no clear understanding of animal welfare expectations was ever obtained; or new policies have been implemented that do not align with institutional expectations, to name a few.

An institution in such a situation faces several risks. In addition to the fundamental ethical concern regarding the welfare of the animals used in the project(s), there can also be an erosion of employee and public trust, increased costs and loss of innovation, decreased reproducibility of the resulting research data (and thus nonadherence to the principles of the 3Rs due to wastage of animals), fewer resulting publications, and reduction or loss of funding. Due to the severity of these consequences, each institution engaged in an international collaboration should be sensitive to the changing environment of the collaborator and have a plan in place that describes an exit strategy, should the need arise.

## Examples of Differences in Supporting Animal Welfare

Three program areas are described here to underscore the fact that institutions considering international collaborations should investigate animal care and use program operations in detail, as there is a lack of consistency across countries in program operations. The institution should be aware of differences in standard practices as part of a gap analysis for its culture of care.

### Ethical Review

An ethical review of proposed animal-based research is not a requirement of all countries' regulatory framework. Even in countries that have animal welfare laws, research animals are often not a specific consideration of those laws. It should be noted that in countries where ethical review is required, there is a varying detail regarding how that ethical review is conducted (ie, does it include the 3Rs, humane endpoints, training

requirements, harm-benefit analysis, pain mitigation, etc.). Who is assigned responsibility for ethical review differs around the world. For example, it may occur at a national/regional level or a local (institutional) level. The autonomy of and authority for the review process can also vary. In the United States, the IACUC's decision cannot be overturned by the institutional official. However, in Japan the IACUC reviews the protocol and submits a report to the director of the institution, who then determines if the work will be conducted (ie, the IACUC has an advisory role rather than functioning as the decision-making body).[35] In India, a fourth R—rehabilitation—of some species of animals (eg, nonhuman primates and dogs) after use in research must be addressed by the principal investigator as part of the research proposal.[36]

### Animal Husbandry

While basic animal care is generally consistent across countries, specific aspects that are fundamental expectations in some countries are not necessarily considered as important in other countries. In an analysis of data from site visits around the globe, AAALAC International has documented that animal environment is the most common nonconformance with AAALAC standards (data from 2014–2016), comprising 25% of all items that must be corrected (ie, mandatory deficiency) to be granted full accreditation. Husbandry, and more specifically behavioral and social management, accounts for a significant portion of these findings. AAALAC data show that animal behavior and social management was ranked the third most commonly cited mandatory deficiency, and over one-half of the mandatory deficiencies in the category of animal environment were related to social housing deficiencies. Thus, institutions should be clear regarding expectations for how animals are housed to promote their well-being (eg, environmental enrichment, social housing of social species of animals, etc.), which is typically based on an assurance that the species-typical behavior of the species considered for use is well understood and accommodated.

### Veterinary Care

Although there is an expectation for veterinary care of research animals in OIE member countries,[32] around the world, there are significant regional differences in training, knowledge, and skill-sets of veterinarians overseeing research animal care and use.[37] This can range from an expectation of one to several years of veterinary postgraduate specialization in laboratory animal medicine to no additional veterinary training requirements following graduation[38] to no specific requirements for veterinary oversight of research animals.[37,39] Competent veterinary support is essential for monitoring research animal welfare, and veterinarians can also provide critical input during study development and planning to promote a 3Rs approach. Expectations for veterinary care and authority, and a review of the availability of competent veterinary support, should be discussed as part of any international research collaboration involving animals. Wherever possible, conflicts of interest in veterinary care should be avoided to ensure data integrity. For example, veterinary researchers and collaborators and their graduate students should avoid taking on designated veterinary roles within their own studies.

## Harmonization Efforts and Outcomes

There are numerous influences on globalization and the associated need to harmonize research animal welfare standards. Perhaps most dynamic among these is the economics of the country. Prior to the "Great Recession" of 2008, there was an economic boom in biomedical research, with the establishment of preclinical research facilities by multinational companies all around the globe, outsourcing of R&D, and numerous collaborative arrangements. Immediately following the drop in global stock markets, multinational companies that conducted preclinical R&D downsized and consolidated their operations. Today, contract research organizations (CROs) are increasingly busy in filling the void that resulted as well as supporting smaller R&D organizations. Therefore, even though the landscape has shifted regarding who is conducting animal-based research, the reach is still global and the need for harmonization of animal welfare standards and practices is still an imperative.

### Who Is Involved

Several organizations with international scope contribute to harmonizing the main features of animal care and use programs and the standards of research animal welfare. Each has a niche that cumulatively results in elevated research animal welfare globally.

#### *Organizations That Establish Guidelines*

**Federation of European Laboratory Animal Science Associations (FELASA)** FELASA (www.felasa.eu) was established in 1978 to establish common standards for training of individuals in laboratory animal science in the EU as well as to develop forward-thinking guidance and policies to harmonize care and management of laboratory animals, with a strong emphasis on the 3Rs. The organization functions by establishing working groups of EU experts to examine specific topics and guidance is developed by consensus. On some issues, FELASA may partner with other organizations, such as the American Association for Labratory Animal Science, to further strengthen its recommendations.

**International Council for Laboratory Animal Science (ICLAS)** ICLAS (www.iclas.org) was conceived of over 60 years ago as an organization to promote and coordinate the development of laboratory animal science around the world.[40] In more recent years, ICLAS has prioritized active promotion of ethical practices, access to education, improving animal quality, and harmonization of standards of care of laboratory animals. In this latter area, in an effort to support its member organizations, ICLAS has adopted or developed guidelines related to humane research endpoints, euthanasia of research animals, education and training of those involved in animal research, ethical review of research animal protocols, and production and maintenance of genetically altered animals.[41–43]

**Institute for Laboratory Animal Research (ILAR)** ILAR (www.ilar.org), part of the Division of Earth and Life Sciences at the US National Academies of Sciences, is responsible for maintaining and updating the *Guide for the Care and Use of Laboratory Animals*.[44] The *ILAR Guide* is an internationally accepted reference document on research animal care and use that was first published in 1963 and has undergone periodic updates, the last occurring in 2010. It is used around the world as a basis for countries, regions, and institutions to develop national standards and ethical approaches for overseeing research animal care and use. Recommendations in the *ILAR Guide* are largely based on published evidence and promote a performance-based approach to animal care. This flexibility in developing processes for harmonized outcomes has made it an invaluable resource for developing and evaluating animal care programs around the world.

**OIE or World Organisation for Animal Health** A framework for regulatory content that addresses basic research animal welfare has been developed by the OIE (www.OIE.int). Chapter 7.8 (Use of Animals in Research and Education) of the Terrestrial Animal Health Code contains several themes and specific recommendations for how its member countries should craft their standards.[32] The OIE notes that the framework may be "delivered through a combination of national, reginal and institutional jurisdictions and both public and private sector responsibilities should be clearly defined." These include implementing the 3Rs, having an oversight system that is governmental or other, conducting a harm-benefit analysis, ensuring an ethical review process is in place, conducting postapproval monitoring to ensure animal activities conform with the approved protocol, performing facility inspections by the oversight body(ies), requiring consideration of humane endpoints in the experiment, ensuring training and competency of personnel, providing a program of adequate veterinary care, ensuring an appropriate source and type of animal for the protocol, ensuring an appropriate physical facility an environmental conditions for the animals and the research, providing good husbandry practices, and transporting animals in a manner that minimizes stress from the journey.[32] Additional guidance on specific topics, such as global harmonization of veterinary training and competency,[45] has resulted from the issuing of the OIE standards.

#### *Organizations That Promote Training*

**International Association of Colleges of Laboratory Animal Medicine (IACLAM)** IACLAM (www.iaclam.org) is a global organization of colleges of laboratory animal medicine, and one its key objectives is to foster training and education of laboratory animal veterinarians to promote the welfare and responsible use of laboratory animals.[40] IACLAM members are also active in examining standards for laboratory animal care as well as veterinary curricula in laboratory animal medicine.[39,46,47]

**World Veterinary Association (WVA)** The WVA is a global association of associations representing over one-half million veterinarians in 90 countries or regions around the world (www.worldvet.org). The WVA has Observer status within the OIE and has developed memoranda of understanding with a number of global entities, including the OIE, Food and Agricultural Organization of the United Nations, World Health Organization (WHO), and World Medical Association (WMA), to support the role of the veterinarian in promoting animal health and human and animal well-being around the world. One of the WVA's key educational objectives is to ensure Day One competencies of veterinary graduates everywhere (http://www.worldvet.org/uploads/docs/wva_policy_on_day_one_competences_march_2017_new.pdf) as well as ongoing opportunities for high quality continuing professional development of graduate veterinarians. Consistent education and training of veterinary graduates will permit better implementation of the OIE's basic standards for research animal care in all countries, ultimately, improving research animal welfare.

#### *Confirming Implementation of Animal Welfare Standards Across Country Borders*

**AAALAC International** AAALAC International's mission is to promote the humane treatment of animals in science through confidential, voluntary accreditation of animal care and use programs (www.aalac.org). AAALAC's accreditation process (described in the association's "Rules of Accreditation") includes an extensive internal review conducted by the institution, which is summarized in an animal care and use program description and on-site assessments by expert peers conducted every 3 years. In this manner, AAALAC observes first-hand how well an institution is conforming with its national/regional/local regulations, policies, and guidelines as well as AAALAC's standards. AAALAC supplements its accreditation program with an extensive education and outreach program that is intended to inform global audiences regarding contemporary, internationally accepted research animal welfare standards. AAALAC International accredits more than 1000 programs in 47 countries using these high standards and a performance approach that encourages continuing improvement in the participating institutions.

### The Impact of Harmonizing Animal Welfare Standards

Harmonization has been described as "to bring into consonance or accord" (Merriam-Webster dictionary), "to be in harmonious agreement" (Wiktionary), or "to be in agreement in action, sense, or feeling" (Dictionary.com). As the biomedical research enterprise continues to span the globe, it is incumbent on the scientific and veterinary medical communities to partner in harmonizing standards of research animal welfare. Varying standards for animal care and use render the comparison of data from animal studies more challenging, can impede reproducibility, delay scientific collaborations, and potentially impact trade between countries.[41] In addition, different journals may impose further welfare standards on manuscript submissions that could forestall publication of key scientific information. Thus, harmonization of research animal welfare standards could have a far-reaching and significant impact on the use of animals in science and the resulting benefits to the animals themselves and society. As early as the mid-1990s it was recognized that harmonization: "1) optimizes the quality of science; 2) addresses the need for similar standards to govern the care and use of animals in international research protocols, thereby bringing a degree of equivalency to the data or information generated; 3) facilitates the movement and exchange of research animals and animal products; and 4) addresses the need for efficiency in costs of research."[48] The minimization/elimination of experimental confounding variables and the resulting comparability of studies has a direct impact on reducing the number of animals used worldwide for research—an outcome consistent with the goals of the 3Rs. In addition, such harmonization leads to refinements of animal care and use practices—an additional outcome consistent with the goals of the 3Rs. In this manner, both animals and science benefit from harmonization. Therefore, reduced duplication of research, more reliable data, meaningful improvements in human and animal health and well-being, reduced costs, an accelerated pace of research, and greater public support for animal-based research are all possible outcomes of harmonized and quality research animal welfare standards.

## Is Global Harmonization of Animal Welfare Standards Achievable?

If harmonization is to be achieved on a global scale, communication of appropriate care and use standards and refinements/alternatives to specific animal procedures needs to occur. Inadequate communication can result in disparate and contradictory approaches to both animal care and animal procedures.

Inadequate information provided to program personnel can lead to misunderstandings and errors in judgment, which in turn can result in flawed research data, reduced animal welfare, increased research costs, and increased regulations. Interactions among researchers (often from varying scientific disciplines), veterinarians and the animal care staff, regulators, and stakeholders are key to this process of communication/information exchange. The increasing online availability of research animal welfare guidelines from several countries around the world, as well as information regarding best practices (eg, the Federal Demonstration Partnership's Compliance Unit Standard Procedure Sharing Site), alternatives, and other refinements to animal research can contribute significantly to harmonizing animal care and use procedures, with both the quality of the research and welfare of the animals benefiting from this harmonization. Recognizing the value of communicating with colleagues, and actively participating in such dialogues, can further advance productive harmonization efforts.

In addition, the implementation of harmonized animal welfare standards must be confirmed "on the ground." This is optimally achieved through a shared responsibility between internal and external oversight systems. Such confirmation ensures that what is written in policies and guidelines is actually occurring in the program. The translation of written goals and descriptions into reality requires assurance that adequate resources are made available to the program, that there is a clear understanding among personnel of their individual roles and responsibilities, that there is a transparent and collaborative relationship among staff at different levels of the organization, and that upper management provides ongoing and visible support for a high-quality program. When institutions and individuals at those institutions adopt a culture of care attitude and are vigilant about maintaining it, global harmonization of research animal welfare is achievable.

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