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Literature Review: What guidance exists for conducting research/studies on or with animals?

The following is a summary of literature that was reviewed in advance of the Think Tank. Literature fell into seven categories: laboratory animal research, clinical studies using privately owned animals, novel veterinary treatments, studies (laboratory or clinical) to benefit other animals, wildlife in research, veterinary ethics, and human research. This summary was created with an eye toward developing guidelines for introducing novel interventions or treatments in "field" settings. It is thus limited to portions of publications that provide insights on and strategies for advancing this animal welfare issue. Although the literature reviewed does not include all relevant resources, we believe that the documents reviewed are representative of current literature.

Laboratory animal research

Most animal research guidelines focus on a laboratory setting. They overtly or tacitly state that research is conducted to benefit humans, with minimal to no benefits to the animals themselves. This is but one way in which research in laboratory animals differs from the research/innovation that is the focus of this Think Tank.

Several publications discuss Ethical Review or Animal Ethics Committees; some target shortcomings. One criticism is that the "ethics of principles" (a utilitarian analysis) tends to dominate the "ethics of consequence" (considering the result of an action or absence of an action) when committees navigate ethical dilemmas regarding animal research (de Boo et al. 2005). Another article asserts that in Institutional Animal Care and Use Committees (IACUCs), the scientific question being researched takes precedence over the welfare of the animals; this is positioned as the opposite of research protections afforded to humans (Ferdowsian 2011).

Multiple publications addressed the "3 Rs"—replacement, reduction, and refinement—which have been a critical concept in animal research since being introduced in the late 1950s. Several publications challenged the 3 Rs as a measure of making animal research more "ethical." One problem identified is that the "Rs" are often considered separately rather than as a unit, and changing one can have a negative effect on the others (de Boo 2005, Ferdowsian 2011). How to prioritize when the Rs are in conflict has received inadequate attention in written guidelines (de Boo 2005). In addition, there is criticism of how individual "Rs" are currently defined and applied—e.g., for "refinement," changing specific research protocols rather than addressing the suffering that individual animals experience during their lifetimes (Ferdowsian and Merskin 2002, Buchanan-Smith et al. 2005).

Several publications propose alternatives to the 3 Rs. Vorstenbosch (2005) and Wolfensohn (2015) recommend focusing on positive animal welfare, and Graham (2015) advocates that research permit "flourishing" and "self-realization," rather than simply avoiding suffering.

Kantin and Wendler (2015) urge respect for dissent, and when possible soliciting assent, of animals in research. New tools to help map and quantify animal welfare levels (physical, psychological, environmental, procedural, and longitudinal) are also presented (Wolfensohn et al. 2015).

Two articles that were reviewed offer novel comprehensive requirements. One presents a "middle-ground moral perspective" with three conditions that must be met to conduct morally responsible/justified animal research: 1) expectation of sufficient net benefit of research, 2) worthwhile-life condition for animals, and 3) no-unnecessary-harm/qualified-basic needs condition. The first requirement sets a demanding standard for morally responsible animal research, the second sets a demanding moral baseline, and the third places demanding limits on suffering, confinement, and death that research animals can experience (DeGrazia and Sebo 2015).

The second article establishes five requirements that are together intended to elevate the threshold for conducting animal research: 1) estimate the pain, distress, and other harms likely to be experienced by animal subjects from birth to death, and report on whether animals appeared willing or unwilling to participate in study; 2) provide sustained ethical justification for the experiment (not just referencing IACUC approval); 3) provide evidence that the experiment is scientifically necessary, not just a potentially useful addition to the literature; 4) explain why this or an analogous study cannot be conducted in consenting human subjects; and 5) explain why a relevant study that could not be conducted in humans would be ethically justifiable in animals (Ferdowsian and Gluck 2015).

There are no doubt additional resources available that propose novel approaches to the welfare and ethical considerations of animal research.

Clinical studies using privately owned animals

Studies conducted with privately owned animals in veterinary schools or practices can directly benefit the species (if not individual animal); they also offer a comparative model for human medical treatments (e.g., with oncology protocols). Several articles cite confusing or inadequate regulatory oversight and ethical review, as well as inadequate "best practices," for clinical trials with pets. (Baneux et al. [2014] state that ethical review of studies with privately owned animals is left up to the individual institution in the U.S., whereas the UK has seen efforts for a more streamlined approach.) Russow and Theran (2003), who discuss the role of the IACUC in addressing ethical problems outside the laboratory, argue that human/companion animal relationships create unique moral obligations to animal owners in a research context.

Several themes were raised in this cohort of literature:

- Protection of the veterinarian/client relationship (Hampshire 2003)
- Informed consent (Russow and Theran 2003, RCVS/BVA Working Party 2013, Baneux et al. 2014, Burton and Khanna 2014, Page et al. 2016)
- Preserving the option of voluntary withdrawal (Russow and Theran 2003)
- Appropriate trial design and good clinical practice guidelines (Burton and Khanna 2014)
- Need to publicize results in order for a study to be ethical (RCVS/BVA 2013)
- Data safety monitoring (Burton and Khanna 2014)

- Use of a placebo/control group, and how they are complicated by a veterinarian's responsibility to provide the highest standard of care; non-malfeasance is a principle that protects human research subjects and, e.g., sham surgery constitutes malfeasance (Russow and Theran 2003, Baneux et al. 2014).
- The effect of research on the general public when performed outside the lab, and the importance of considering the public's reaction as an indicator of ethical values and concerns (Russow and Theran 2003)
- Prevention of "unnecessary" pain or distress (Hampshire 2003), including establishing the pain threshold required to undergo ethical review as "that of introducing a hypodermic needle though the skin" (RCVS/BVA 2013)
- Client/owner vulnerability and safeguard from consumer fraud (Hampshire 2003)

Page et al. (2016) attempt to adapt existing guidelines for conduct and oversight of clinical trials in humans to veterinary trials, detailing five best practices: study design, approval policies, consenting process, post approval monitoring, and reporting and publication. The paper also addresses what is needed and expected of different stakeholders.

The RCVS/BVA Working Party (2013) released a publication addressing the increase in clinical research falling outside the Animal Scientific Procedures Act. It discusses methods to ensure an ethical study and access to ethical review; the authors suggest that RCVS establish a national standing for ethical review of practice-based research and outline what to consider in an *ad hoc* committee.

Novel veterinary treatments

Novel veterinary treatments are related to clinical trials. Drawing on British Small Animal Veterinary Association (BSAVA) committee meetings, two articles address clinical use of novel therapies (including surgical procedures, medical treatments, or behavioral interventions). The guidance is a response to the lack of specific regulatory control over novel veterinary treatments in a clinic setting. One key difference between novel clinical procedures and "scientific" procedures is that the only benefit relevant in veterinary practice is patient welfare (Yeates et al. 2013). The authors differentiate "novel" from "accepted" procedures, making a good contextual point that novel therapies need not be extreme, and many accepted therapies are invasive and risky.

Ethical guidelines and requirements discussed in combination in the two articles (Yeates et al. 2013, Yeates 2015) include:

- *Individual animal welfare*: decisions should be based on the welfare of the animals directly affected; patients should not receive treatment solely to advance medical or veterinary science.
- *Clear expectations, thresholds, and objectives, including anticipated risks and benefits*: these parameters help clinicians/owners weigh harms vs. benefits and evaluate quality of life, and also allow clinicians to predict expected upper levels of harm and make judgments about justification and required ethical scrutiny. The authors emphasize the need to make predictions based on evidence from other species/application of accepted scientific principles, and to rely on consistent definitions.

- *Knowledge of alternative therapies*: veterinary professionals considering novel treatments should be aware of previously and currently used therapies and evidence relating to the novel therapy.
- *Minimizing harms*: Treatments should be designed to minimize suffering and involve as little pain, discomfort, fear, risks, etc., as possible, plus first be trialed in vitro/on limited numbers of animals.
- *Appropriate personnel and avoiding conflicts of interest*: Specialists may be beneficial for procedures that deviate from accepted procedures, but it is unnecessary to limit novel procedures to specialists as a matter of course.
- *Owner consent*: An owner must consent to treatment (with support of evidence, transparent information from the veterinarian, and no undue influence or financial incentives), and at the same time cannot mandate a clinician to provide treatment. (With relevance to the Think Tank, authors note that "Stray and feral animals of domestic species should not be used in procedures, except if there is an essential need for a novel treatment for that animal [i.e., in the best interests of an individual animal or of that group])."
- *Authorization*: Ethical oversight is needed when utilizing novel treatments.
- *Real-time assessment*: It is important to have ongoing assessment and refinement and contingency "rescue" plans given lack of data and "risk of overestimating benefits."
- *Retrospective assessment and publication*: Novel treatments must undergo retrospective assessment and publication of results, regardless of outcomes, in a peer-reviewed journal.
- *Humane end points*: There should be a contingency plan and humane end points for any novel treatment.

Studies (laboratory or clinical) to benefit other animals

A handful of funders/organizations founded for the benefit of animals (veterinary care, health, and/or welfare) have published policies/guidelines on the use of animals in projects that they fund, or for work presented at conferences that they organize. Although this subsection overlaps with the previous three, it has its own subsection because of the specificity of the policies and potential relevance to those created for field studies.

We reviewed Morris Animal Foundation, Found Animals Foundation/Michelson Prize & Grants Program, and World Small Animal Veterinary Association (WSAVA) policies. These guidelines frequently defer to standard practices for animal welfare (e.g., governing animal ethics committees/standards, 3Rs, and/or the argument that research must be "good" in order to be ethical). However, some of the guidelines also address topics that appear to exceed conventional standards for laboratory animal research—e.g., avoiding terminal endpoints and placing animals for adoption or in sanctuary following research. The Michelson Prize & Grants Program acknowledges ethical concerns about involving animals in research but concludes that dog/cat health, well-being, and "overpopulation" justifies research.

Wildlife in research

Guidelines for research in wildlife are relevant from the standpoint of considering research in field conditions and with unsocialized and "unowned" animals; particular correlations exist for research involving free-roaming/feral cats. Publications identify a variety of potential beneficiaries of wildlife research: the individual animals taking part in research, other animals of their species, other species of animals, and the environment (including humans) more broadly.

American Society of Mammologists (ASM) guidelines for use of non-domesticated mammals in research state that fieldwork is the most difficult issue for ethical review committees that typically evaluate laboratory-based studies (Sikes et al. 2011). ASM's discussion of ethics is limited to the 3Rs and dubious advocacy of individual judgment ("Most field investigators already embrace the ethical treatment of animals because of their respect for nature and their dedication to study wild species"). The content and framing is significant and relevant insofar as it reflects a particular conception of "ethics."

Another article, written by a Dutch author, contrasts research in wild species in biological field research and laboratory animals in biomedical research. This publication cites tangible aspects of wildlife research that are not applicable to laboratory animals and addresses natural versus experimental suffering (criticizing use of suffering in nature as justification for suffering in research). The paper proposes "natural functioning" (a wild animal's ability to function naturally and autonomously) as a co-occurring standard for animal welfare in wildlife research.

Publications address a handful of ethical and practical considerations for field research. The Association for the Study of Animal Behaviour (ASAB) (2012) emphasizes the importance of considering the entire environment (human and animal) when conducting research and weighing potential gain versus cost, the fact that research in a field can have impacts on places other than the location of the study, and the role of positive reinforcement.

Several publications specifically address marking and identification of animals, which has direct applications to ACC&D's marking work but differs insofar as wildlife are not connected to a human community in the same way as, e.g., free-roaming owned dogs. Public perception and the objective of demonstrating humane treatment in order to positively affect human care of and behavior toward the animals are a lesser part of the equation. Instead, the "human element" is primarily limited to health and safety.

ASAB (2012) advises that wildlife marking should be pursued only after considering other ways to identify animals (phenotypic, feces). A publication on use of measuring devices on wild animals (which assumes that the device benefits knowledge about ecology or a wildlife species vs. benefitting an individual animal) advocates for better quantitative measures on the effects of a device (Wilson and McMahon 2006). Three specific points are relevant to ACC&D's work. First, the authors advise using "discomfort," not "suffering" or "pain," because it represents a broad dynamic range, carries less inherent bias, and can be qualified with terms such as "extreme" or "mild." (The "discomfort" discussion did not focus on device application per se.) Second, the authors advise considering the survival probabilities of marked animals, plus the effects on non-treated animals. Third, the authors note that capture without reward is one of the most stressful things a wild animal can experience (relevant for feral cats/unsocialized dogs) and can carry long-term consequences. They argue that this underscores need to minimize stress and makes a case for use of sedation with an amnesic effect.

The recommendation of sedatives contrasts with other protocols. Specifically, in discussing ear punching and toe clipping, ASM (2011) states, "anesthetics and analgesics generally are not recommended because prolonged restraint of small mammals to administer these substances and

consumption of the analgesic substances...via licking likely cause more stress and harm than conducting the procedure without their use" (pp. 245-6).

Veterinary ethics

Morgan and McDonald (2007) address ethical questions and tensions surrounding treatment of pets, as well as strategies to communicate with owners about them. Tensions, the authors argue, stem from the fact that veterinarians have a wide range of responsibilities and accountability (animals, owners, the profession, public). The authors differentiate between "moral" and "practical" dilemmas in veterinary medicine and discuss four specific sources of ethical tension:

- Differences in beliefs regarding the importance of animals (e.g., anthropocentric vs. biocentric);
- Differences in beliefs regarding responsibilities to animals (how much care is owed to animals generally, and to different "categories" of animals specifically -- e.g., "found" vs. actively acquired);
- Different assessments of what is in an animal's best interest; and
- Conflicting interpretations of a veterinarian's role (veterinarians as advocates for patients vs. serving client's best interests, what information should be disclosed to patients).

McDonald (2010) lists steps and questions to aid veterinarians in moral decision-making (though the questions are also applicable to other professions): 1) Recognize the moral dimension, 2) identify the interested parties and their relationships, 3) identify the values involved, 4) weigh the benefits and the burdens, 5) look for analogous cases, 6) discuss with other relevant parties, 7) determine if the decision is in accord with legal and organizational rules, 8) and answer the question "Am I comfortable with this decision?"

Morgan and McDonald (2007), McDonald (2010), and an educational module for veterinarians (Institute for Healthcare Communication/Bayer Healthcare Animal Health 2008) are distinct from other resources reviewed insofar as they rely heavily on methods (role playing, questions, communication skills) that can be taken directly into field contexts.

Human research

Research on humans was included in the literature review for two main reasons. First, there are corollaries between research on animals and research on humans who cannot personally consent. Second, research on humans addresses issues of exploitation, recruitment, incentives, vulnerable communities, and power differentials, all of which can be applicable to field-based work.

Primary principles underlying ethical research with or on humans are respect for persons (including respect for autonomy and protection of persons), non-maleficence (minimizing harm), beneficence (maximizing benefits), and justice (Path 2002, Fischer 2006). There are multiple formalized principles, standards, and committees focused on ethical research involving humans (e.g., Belmont Report, Declaration of Helsinki, Nuremberg Code, National Bioethics Advisory Commission), as well as ethics committees (Institution Review Boards) in individual institutions.

Several articles discussed issues, gaps, and questions specific to conducting research in developing countries. Points with relevance to animal studies, particularly in developing countries, include:

- *Host country contexts*: The need for strengthened capacity in research ethics, particularly a deeper understanding among researchers of the social, economic, and political contexts of trials in developing countries (Singer and Benatar 2001)
- *Incentives*: Specification that incentives should not be equated with coercion (Benatar 2002)
- *Informed consent*: The importance of effective communication to ensure legitimately informed consent and avoid situations where subjects feel like they have no choice but to participate in a study (Benatar 2002), and "5 Benchmarks" for evaluating informed consent (Emanuel et al. 2004). One principle of Good Clinical Research Practice is that permission of a community leader or other authority cannot substitute for individual informed consent (World Health Organization [WHO] 2005).
- *Quality study design and data*: A study requires robust data and study design, and ability to produce scientifically reliable results, to be ethical (Emanuel et al. 2004, WHO 2005)
- *Ethical review*: The common failure to conduct ethical review of human research in developing countries and perceived cultural insensitivity of United States IRBs, highlighting the need to address both possibilities in pursuing any research internationally (Hyder et al. 2004); also, the importance of having lay members, particularly women and vulnerable participants, as participants of an ethics committee in the country of research (Nuffield Council on Bioethics 2002).
- *Conflicting ethics*: Which or whose ethics should be used when one country, usually Western, does research in another, usually non-western? What happens when they conflict? (Christakis 1992).
- *Community engagement*: The importance of community engagement in developing countries, the fact that failure to engage communities can undermine research, and key components of community engagement (Tindana et al. 2007).
- *Ensuring that vulnerable populations benefit from research*: The extent to which vulnerable populations benefit very little from much of the research in which they participate, and strategies to change this paradigm (e.g., development of such concepts as "fair benefits" and "ancillary care," linking research to improved healthcare and greater social justice) (Benatar and Singer 2010).
- The need for investigators to meet standards of host-country scientific and ethical committees, the collaborating institution, and donor alike, and the need for the benefits of knowledge resulting from a study to be available and affordable for the host country to avoid "a violation of the principle of justice" (Barry and Molyneux 1992).
- *Standard of care*: It is argued that the appropriate standard of care when conducting human research in developing countries is not adequately defined; Benatar and Singer (2000) advocate for accounting for the social, economic, and political contexts in which a study is taking place and offer practical recommendations for making moral progress in international health research—e.g., involving members of host country in study design and implementation, ensuring that trials have direct relevance to health needs of the host country, and providing subjects with care or treatment they would not normally get.

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