Association of Primate Veterinarians Lifetime Use Guidelines for Nonhuman Primates in Biomedical Research

Purpose

Individual research protocols in the United States must include humane endpoints, as required by the Animal Welfare Act11 and The Guide for the Care and Use of Laboratory Animals.9 The Association of Primate Veterinarians has published guidelines to assist veterinarians and institutions in developing humane endpoints for nonhuman primates (NHP) in biomedical research.1 While there is study-specific guidance, there is currently insufficient guidance or data regarding a maximum lifetime limit or methods to establish a limit for research use of NHP. The purpose of this document is to advocate for the establishment of institutional policies pertaining to lifetime limits for use of NHP participating in animal research. Benefits derived from this effort include improvement of animal welfare, reduction of experimental confounds associated with stress, prevention of overuse of animals that have sufficiently participated in research efforts, and potential reduction in total number of animals used. These guidelines are intended to assist institutions in developing policies to determine the maximum number of research procedures an animal should participate in and when an animal should be permanently removed or ineligible from participating in further research studies.

Background

The justification for using NHP in research typically comes in the form of weighing the costs borne by the animals against the benefits to society that result from the research. While societal benefits of research involving animals are relatively easy to ascertain, the costs to the animals are more difficult to assess. Ultimately, these costs, or the ‘research load,’ from the perspective of each animal need to be considered, especially in the context of animal supply shortages. The ‘reuse’ or ‘recycling’ of individual NHP is a significant problem, both ethical and scientific, that will likely become more prominent in the future as the supply of NHP is projected to dwindle due to limited local breeding programs, export restrictions, and transportation obstacles, together with continued growth of research demand. Due to these factors, research institutes may become more likely to re-use animals for multiple projects, resulting in increased long-term costs/harm to the animals.

Critical reviews of all animal study protocols are performed by the Institutional Animal Care and Use Committee (IACUC) or comparable oversight body (OB) within each institution where animals are housed and/or the experiments are performed. The conscientious application of the Three Rs (Reduction, Refinement, and Replacement) by investigators should be scrutinized by IACUC/OB reviewers. The specific impacts to both physical and psychological wellbeing of NHP experimental subjects is typically determined by obtaining expert opinions from behavioral specialists, veterinarians, and investigators with expertise in the field of research relevant to the protocol. Additionally, relevant information about similar procedures published in human medical literature is reviewed and may be used to assess the pain or distress associated with a procedure. Based on these assessments, recommendations for improvements are proposed and modifications made prior to protocol approval. While these activities may help to safeguard animal welfare within each protocol reviewed, there is no codified process for reviewing the cumulative welfare impact of an animal’s participation in multiple studies, as well as the impact of the clinical history throughout their lifetime.

The assessment of cumulative use should include a review of factors that negatively affect an animal’s quality of life. These factors include the duration and invasiveness of procedures performed, as well as contingent factors such as transport, housing type, husbandry practices, opportunities for social contact with conspecifics, and the temperament of the individual animal, as stressors are known to affect individual animals differently.5 Lastly, it should be considered that from the animal’s perspective, discomfort causes a negative impact, regardless of whether the discomfort results from clinical conditions, injuries related to social housing, or research procedures.

Several scoring systems for lifetime stressors have been proposed. Perhaps the most developed thus far is the Animal Welfare Assessment Grid, or AWAG.6,8 “This system was derived from work published by Honess and Wolfensohn in 2010. AWAG is a web-based software application for capturing, storing, and visualizing animal welfare assessment data.” AWAG uses four parameters (Environmental, Procedural, Psychological, and Physical) to calculate an overall Cumulative Welfare Assessment Score (CWAS). While these systems are helpful for subjectively assessing criteria and events that can impact an animal’s welfare, a scoring system that is validated by an objective indicator of stress or suffering is perhaps also needed. For example, the relative impacts of individual housing and major surgery cannot be equated at this time. To address this need, some authors have proposed measuring changes in hippocampal volume by MRI or telomere length reduction as a way to quantify chronic stressors.7,10 These measures could quantify stressors independent of cause; however, these have not yet been validated for this purpose in NHP.

Guidelines

Institutions should formally consider generating policies regarding lifetime use limits for nonhuman primates in research. The assessment may be accomplished by a veterinarian or a committee of people to represent the needed expertise. Committee membership should represent expertise in these areas:

1. Clinical health of the animals
2. Knowledge of the procedures commonly performed
3. Knowledge of the psychological wellbeing of the animals
4. Knowledge of the upcoming research projects and colony demographics

The committee should evaluate each animal’s past research experience and consider the cumulative welfare impact in conjunction with future proposed research use. The committee
should develop a facility-specific strategy to evaluate whether additional research use is appropriate. If additional research use is not appropriate, the committee should develop directives on the future use or disposition of the animal. Topics that may be considered include, but are not limited to:

1. Health status and potential for future research
   a. Animals with a clinical or experimental history (for example, adverse events experienced, exposure to test articles or pathogens) that would preclude further research use should be identified.
   b. Chronic or on-going health concerns and their role in the animal’s welfare and longevity should be factored into additional research use.
2. Total number, frequency, and invasiveness of procedures in proposed new study
3. Exemptions from housing and husbandry standard operating procedures (for example, food or water regulation)
4. Total number of minimally invasive, minor, and major surgical procedures the animal previously experienced
   a. Additional weight may be given to more recent procedures, particularly if they were numerous and/or frequent.
   b. Clinical procedures performed should be considered in addition to research procedures. For example, animals that have undergone major surgery for clinical purposes (for example, laparotomy, caesarean section) may be restricted from participating in any additional studies that require major abdominal surgery.11
5. Current housing status
   a. Housing in large outdoor social groups may be considered a positive impact on welfare supporting on-going use.
   b. Single housing for extended duration may be considered a negative welfare impact that counts against long-term use.
6. Consult relevant APV guidelines
   a. Nonhuman Primate Endpoint Guidelines
   b. Guidelines for Assessment of Acute Pain in Nonhuman Primates
   c. Socialization Guidelines for Nonhuman Primates in Biomedical Research
   d. Guidelines for Post Research Retirement of Nonhuman Primates

Conflicts of interest (COI) should be considered if research staff are involved in assessment of NHP reuse. Recusals should be considered if decisions involve potential COI and have an appearance of favoring reuse of NHP on a particular study. Animals that are determined to be inappropriate for reuse on a specific project may be reevaluated later or may be appropriate for use on a different project. For animals that may not be appropriate for reuse and will be maintained at the institution for the remainder of their life, every attempt should be made to maintain the animal in a stable social setting.

The recommendations presented here are guidelines to assist discussions regarding lifetime use at biomedical research institutions. A future goal for this guidance may include developing a scoring system for various procedures with consensus among stakeholders regarding lifetime limits for research load. To date there are no broadly accepted lifetime limits for any common procedures. We strongly encourage policy makers, accreditation organizations, government oversight bodies, researchers, and animal health and welfare specialists to study and publish data and further guidance that can assist institutions with these decisions. Surveying institutions represented.

References