Association of Primate Veterinarians
Humane Endpoint Guidelines for Nonhuman Primates in Biomedical Research

PURPOSE

The Association of Primate Veterinarians (APV) strongly recommends the use of humane endpoints to prevent, alleviate, or reduce pain and distress in nonhuman primates (NHPs) in biomedical research. Humane endpoint criteria should be developed for every research project to identify when a NHP should be removed from a study, provided with supportive treatment, or euthanized. Humane endpoints should also be developed for all colony NHPs to ensure that animals with untreatable conditions do not experience undue pain or distress and are euthanized in a timely fashion. The purpose of this document is to assist veterinarians who provide care to NHPs and IACUC members in developing appropriate humane endpoint policies within their institutions.

BACKGROUND

Humane endpoints are defined as the points at which an experimental animal's pain and/or distress is reduced, minimized, or terminated by taking actions such as, giving treatment to relieve pain and/or distress, ending a painful procedure, or euthanasia. (CCAC, 1998). Establishing and implementing humane endpoints requires a commitment by the entire research team (e.g., the principal investigator, animal care personnel, behavioral staff, research technicians, IACUC, and the veterinarian). Humane endpoints may differ from experimental endpoints and may need to be implemented prior to an animal reaching an experimental endpoint. The intended goal of developing humane endpoint criteria is to standardize recommendations for interventions based on a defined set of clinical and behavioral criteria that will reduce, alleviate, or prevent pain and distress. This can be accomplished by closely monitoring the animal to determine if it should be removed from the study, provided supportive care, and/or euthanized before the animal experiences unnecessary pain and distress. The Animal Welfare Act requires animal pain and distress to be minimized. The principal investigator should consult with the veterinarian in the planning of procedures likely to produce pain or distress; and the withholding of tranquilizers, analgesics, anesthetics, or euthanasia when scientifically necessary should continue for only the necessary period of time (7 U.S.C. Chapter 54 Section 2143(a)(3)). Although not assigned to an active study, NHPs in breeding colonies or other non-research protocols may also experience pain and distress when their health or quality of life has been significantly compromised. Therefore, humane endpoint criteria should be established for all NHPs held in research facilities and used in conjunction with the professional judgment of the veterinarian.

The establishment of humane endpoints for NHP research must occur prior to the initiation of a study, and may require updating if and/or when an unexpected condition arises. Humane endpoints in animal experiments describe the identification of clear, predictable, and irreversible criteria which substitute for more severe experimental outcomes such as advanced pathology or death (NC3R, 2014). The criteria must be species specific with clinical signs and interventions appropriate for the animal and the protocol procedures. For some studies, management of unrelieved pain remains
problematic because pain-reducing agents cannot be used for scientific reasons (Carstens, 2000). In these cases, animal well-being should be monitored closely at regular intervals, and studies terminated if pain or distress cannot be alleviated. Some types of research (e.g., infectious disease and toxicity) may be associated with high mortality rates or require the production of progressive and severe disease states that may result in death (Toth, 2000). A sound approach is needed to identify and predict when a moribund state may be reached and to remove an animal from research manipulations before this state occurs.

It is a good practice to develop humane endpoint criteria for common clinical situations to remove uncertainty about how animal care and research personnel should proceed in specific situations, as well as promote a culture of compassion. Animals on biomedical research and toxicological protocols may experience pain or distress from induced diseases, procedures, or toxicity to achieve scientific objectives. Ideally, the scientific endpoints are achieved prior to meeting humane endpoints.

Scoring systems are beneficial to monitor parameters of health and welfare and may be used to evaluate each animal for signs of deteriorating physical and psychological health. Types of clinical signs and conditions that may be observed vary from measurable and objective to those that are more subjective (Morton, 2000). Clinical parameters can be objective (e.g., reduced/increased body temperature, absence/reduced appetite or fluid intake, and reduced/increased body weight) and subjective (e.g., changes in behavior, hydration status, or mobility, other deficits, or severity of vomiting/diarrhea). These parameters can be utilized to design scoring systems and identify humane endpoints. Inclusion of objective parameters in the scoring system in most cases contributes to a more vigilant system universally understood and applied by all users. Humane endpoints should be tailored to each study and anticipated conditions that may arise. These endpoints should be reviewed periodically throughout the study to ensure they remain applicable and comprehensive. Timely euthanasia can improve research and scientific validity by enhancing the quality of samples collected, reducing distress and improving animal well-being, and alleviating unnecessary suffering (Stokes, 2000).

Another option which can improve animal welfare is the implementation of quality of life (QOL) committees. These committees are formed when an animal is diagnosed with a terminal disease, debilitating clinical or behavioral condition, or placed on a study in which pain or distress may occur. The QOL committee is composed of members who know the animals well (e.g., veterinarian, behavioral staff, animal care staff, trainers, enrichment technicians, pathologists, and research staff as applicable) and who can assist in developing specific clinical and behavioral guidelines for each animal. Changes in individual animal characteristics/traits are evaluated along with the clinical records to provide comprehensive information to the veterinarian who must determine the endpoint and when to euthanize (Lambeth et al., 2013).

**GUIDELINES**

1. APV strongly recommends research institutions develop guidelines for humane endpoints and implement animal monitoring parameters to prevent, alleviate, or reduce pain and distress in NHPs. APV also supports the formation of QOL committees to closely monitor the behavioral and clinical condition of animals at risk of death due to disease or research endpoints.
2. A moribund condition indicates an animal is in a severely debilitated state and in terminal distress. Moribund condition and death should be avoided as study endpoints (unless there are no alternatives) and must be scientifically justified and approved by the IACUC. Unless scientifically justified and approved by the IACUC, all moribund NHPs should be immediately evaluated by a veterinarian and euthanized.

3. The veterinarian has the authority to euthanize any animal that has become moribund or has reached an IACUC protocol approved humane endpoint. The veterinarian should make every practical attempt to discuss their concerns with the research team prior to taking any action. Under 9 C.F.R. 2.33(a)(2) the attending veterinarian has the appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use. As a result, the veterinarian has the authority to euthanize an animal for humane reasons when professional judgement deems it necessary.

4. For research protocols, researchers must establish clearly defined humane endpoint criteria for all studies using NHPs and these must be approved in advance by the IACUC. Endpoints should be developed by the research team in collaboration with the veterinarian, animal care personnel, and behavioral staff. Whenever possible, surrogate endpoints, such as those developed using various imaging modalities or molecular biomarkers should be used to minimize animal pain and distress.

5. Research and animal care personnel must be familiar with normal NHP behavior and physiology as NHPs are stoic animals and often mask pain. They should be trained to recognize changes in behavior and clinical condition so that they can effectively identify an animal experiencing pain or distress. All observations should be documented and available for review.

6. A humane endpoint scoring sheet is a valuable tool that can be used to monitor and document behavioral and physiologic parameters that are predictive of changes in clinical condition. Endpoint assessment sheets or other similar forms of documentation should be accessible for review, should clearly describe what procedures to institute when a humane endpoint is reached, and should list emergency contact information.

**Examples of Criteria Used for Humane Endpoint Determination***

- A specific percentage of body weight loss (e.g., 20% from pre-study weight or a body condition score <2/5)
- Nonresponsive anorexia of a specific duration (e.g., 4 consecutive days with concomitant significant body weight loss)
- Persistent diarrhea or vomiting unresponsive to treatment
- Nonresponsive medical conditions (e.g., organ failure, respiratory distress, sepsis)
- Profound hypothermia or hyperthermia unresponsive to corrective action
- Serious complications secondary to medical/surgical interventions or other experimental manipulations that fail to respond to corrective action
- Severe self-injurious behavior that cannot be managed with behavioral interventions, medical treatment, and/or study removal
*These represent general examples; specific humane endpoints must be developed within each institution.

REFERENCES

Altweb Endpoints Database
http://altweb.jhsph.edu/resources/refinement/sections/endpoints.html


The Animal Welfare Act 7 U.S.C. Chapter 54 Section 2143(a)(3)


http://www.ccac.ca/english/guidesmw/ch10e.doc


OECD Environmental Health and Safety Publications Series on Testing and Assessment (2000); No. 19, Guidance Document on the Recognition, Assessment, and Use of
Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation.


