

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

The Association of Primate Veterinarians strongly recommends the use of humane endpoints to prevent, alleviate, or reduce pain, distress, and suffering of nonhuman primates in biomedical research. Endpoint criteria should be developed for every research project to identify when a nonhuman primate should be removed from a study, provided with supportive treatment, or euthanized. Endpoints should also be developed for all colony nonhuman primates to ensure that animals with untreatable conditions are euthanized in a timely fashion.

## **APV RECOMMENDATIONS FOR DETERMINING HUMANE ENDPOINTS FOR NONHUMAN PRIMATES IN BIOMEDICAL RESEARCH**

1. APV strongly recommends that each biomedical research institution develop guidelines for humane endpoints and that an animal monitoring policy be put into effect to prevent, minimize, or reduce pain, distress, and suffering in nonhuman primates.
2. To alleviate unnecessary pain and distress, the veterinarian has the authority to euthanize an animal that has become moribund or has otherwise reached a humane endpoint. The veterinarian should make every attempt to discuss their concerns with the research team and IACUC, prior to taking any action.
3. Researchers must establish humane endpoint criteria for all studies using nonhuman primates and these must be approved in advance by the IACUC. Endpoints should be developed by the research team working together with the veterinarian and animal care personnel. Whenever possible, surrogate endpoints, such as those developed using various imaging modalities or molecular biomarkers should be used to minimize animal pain and suffering.
4. Clearly defined endpoint criteria and responsibilities for when and how animals are monitored and treated should be agreed upon prior to study initiation. Examples of endpoints that may be considered are listed below.
5. Research and animal care personnel should be trained to recognize changes in behavior and clinical condition so that they can effectively monitor when an animal's condition changes. All observations should be documented. An endpoint scoring assessment sheet is an invaluable tool that can be used to monitor behavioral and physical parameters that are predictive of changes in clinical condition. Endpoint assessment sheets or other similar forms of documentation should be accessible to both the research and animal care teams. Assessment

sheets should also clearly describe what procedures should be instituted when a humane endpoint is reached as well as emergency contact information.

6. Whenever possible, moribund condition and death should be avoided as study endpoints unless there are no alternatives. Endpoint criteria must be justified and approved in advance by the IACUC.
7. A moribund condition indicates that the animal is in a severely debilitated state and in terminal distress. Unless scientifically justified and approved by the IACUC, all moribund nonhuman primates should be immediately euthanized to prevent further distress or suffering.

#### Examples of Criteria Used for Endpoint Determination\*

- A specific percentage of body weight loss in nonobese adult animals, for example, 15% from prestudy
- Nonresponsive anorexia of a specific duration, for example, 4 consecutive days with concomitant significant body weight loss
- Persistent diarrhea or vomiting of a specific duration with wasting
- Major organ failure or nonresponsive medical conditions, eg, severe respiratory distress, icterus, uremia, persistent pyrexia.
- Profound hypothermia
- Serious complications secondary to surgical interventions that do not respond to medical therapy

\*These represent examples, specific endpoints must be approved by each IACUC

#### **BACKGROUND:**

Humane endpoints are defined as the earliest time at which an animal may experience unnecessary pain or distress, undue suffering, or impending death (CCAC, 1998). The intended goal of developing humane endpoint criteria is to monitor the animal closely and to remove it from the study, provide supportive care, or euthanize it before the animal experiences unnecessary pain and suffering. This goal must be tempered by an understanding that removing an animal from a study or euthanizing it prematurely could jeopardize research results, potentially wasting the life of an experimental animal (USDA, 2002). In addition, nonhuman primates assigned to breeding colonies or other nonresearch-related protocols also reach clinical endpoints when their health or quality of life has significantly deteriorated. Therefore, humane endpoint criteria should be established for all nonhuman primates held in biomedical facilities and used in conjunction with the professional judgment of the veterinarian. Establishing and implementing humane endpoints requires commitment by the investigator, using input from the entire research team, including animal care personnel and the veterinarian. The proposed APV guidelines will assist veterinarians, who provide care to nonhuman primates, to develop appropriate endpoint policies within their institutions.

The establishment of humane endpoints for research involving nonhuman primates must occur prior to the initiation of a study and discussions should involve the veterinarian, the research team, animal care personnel and the IACUC. Developing endpoint criteria for common clinical emergencies also helps to remove uncertainty about how animal care and research personnel should proceed in specific situations as well as promoting a culture of compassion for the animals being kept. Animals used in biomedical research and testing may experience pain or distress from induced diseases, procedures, and toxicity. Ideally the humane and scientific endpoints occur at the same time and whenever possible, the criteria should lead to termination of the study before the onset of pain and distress.

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 and at regular intervals and studies terminated if animals cannot be made comfortable. Some types of research, such as infectious disease challenges, are 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 when this state occurs. In many cases, allowing an animal to die is counterproductive to the nature of the research being performed and little additional information is obtained..

A scoring system is beneficial to monitor parameters of health and welfare and can 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). Parameters such as marked behavioral changes, reduced body temperature, changes in body condition score or hydration status, severe unremitting vomiting or diarrhea, inability to ambulate, prostration, prolonged anorexia, and severe weight loss can be monitored to identify study endpoints. Endpoints should be tailored to each study or condition. 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).

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