Humane Endpoints

In the context of animal-based research, endpoints are criteria that serve as the basis for ending an experiment or test. Humane endpoints intend to avoid or minimize research animal pain or distress while still attaining the study objectives. Ideally a humane endpoint corresponds to that point in time when the scientific objectives of a study have been met without any associated pain and/or distress. If that is not possible, humane endpoints can still reduce the severity and/or duration of pain and distress experienced by animals. To the greatest extent possible, well-defined criteria for preemptive euthanasia should be advocated as the humane endpoint of last resort before any animal is likely to progress to an agonal state and eventual death. Humane endpoints are an ethical component of responsible research and a fundamental expectation of regulatory agencies, funding entities, and the public.

All mitigation strategies should be considered to eliminate or reduce sources of pain, distress, fear, and anxiety that could contribute to a negative affective state in the animals. Such strategies may include but are not limited to: stress-reducing techniques for handling and restraint; acclimation strategies; anxiolytics and/or analgesics; positive reinforcement training; imaging, laboratory biomarkers, and other early-stage indicators of experimental disease and injury progression or reversal.

Considerations for endpoint optimization

If pain or distress is possible or expected, humane endpoints should be identified in advance of the study and discussed with a laboratory animal veterinarian during development of animal study proposals.

The earliest possible endpoint compatible with the scientific objectives of a study should be clearly identified. Likewise, parameters used to define that endpoint should be evidence-based, consistent with applicable animal welfare and scientific concerns, and reproducible by other investigators. Endpoints must consider both the degree of severity and the duration of pain or distress. There is an obligation to consider all types of information available through published literature, retrospective studies, and the experience of peers in the planning phase of a study. If historical information is not available, pilot studies utilizing a limited number of animals can assist in establishing the time course of events to predict when animals require more careful monitoring for intervention as appropriate.

The opportunity to compare reactions of control animals to those of treated animals can help to identify ordinary clinical changes, such as alterations in behavior, body temperature, body condition, and weight-loss patterns, that can serve as objective indicators of pain, distress, and discomfort. However, care should be taken to use the appropriate size for control and treated groups to achieve the study objective, which does not necessarily mean these groups need to be the same size.

It may be helpful to invest in obtaining additional observations, parameters, and biomarkers for future refinement of endpoints. When such data are published, they have the potential to benefit the entire biomedical research community.
Even in studies where scientific justification precludes pharmacologic interventions, supportive veterinary care may be an option that can significantly improve the welfare of study animals as well as empower care staff to mitigate compassion fatigue. Provision should be made in the planning phase of the study to ensure animals are readily able to access food and water throughout the study, are kept at appropriate temperature and humidity to compensate for loss of homeostasis, and that primary enclosure furnishings provide as much comfort as possible. Examples include gel diets, supplemental fluid therapy, more palatable or more easily ingested diets (i.e. powdered or softened) and caloric supplementation, extra bedding or soft surfaces, additional warmth for hypothermic animals, and nursing care to maintain hygiene.

Observation periods should be at a frequency that provide timely identification of animals approaching endpoint criteria. Through establishment of appropriate thresholds for clinical signs, behavior and other measurements, documentation of these thresholds in a written study proposal and close collaboration with the veterinarian throughout the planning and execution of the study, clear expectations are communicated to all personnel. This improves oversight and allows appropriate interventions, which are designed to minimize pain and distress. Strategies for optimizing such oversight include using previously obtained data to predict clinical progression, and scheduling experiments so that endpoints are not reached during periods of reduced staffing (such as evenings/nights, holidays, and weekends), as well as increasing observation frequencies with clinical progression. Preemptive planning for on-call schedules ensures availability of trained staff for potential interventions after-hours. Use of remote monitoring methodologies may be employed, such as simple, low-cost cameras, or more advanced systems that record physiological, behavioral data, or activity monitoring.

Those involved in research and care of the animals should be trained to recognize species-specific signs of pain or distress, which may include subtle changes in behavior and other parameters.

**Documenting parameters for endpoint evaluation**
Recorded assessments using a scoring matrix may be considered and allows an objective and cumulative assessment of pain and distress for documentation and easy review by veterinary staff.

**Documentation and approval of activities using endpoints**
Endpoints should be fully described in the submitted animal study proposal and reviewed and approved by the Institutional Animal Care and Use Committee. Humane endpoints must be clearly understood by all IACUC members and to all those involved in the research. Endpoints should be periodically re-evaluated and adjusted to optimize their impact on animal welfare and suitability for the research. Appropriate amendments should be submitted to the IACUC before initiating any changes.

**Selected References**


Stokes, WS (2002). Humane endpoints for laboratory animals used in regulatory testing, ILAR J 43: S31-S38.


Approved by the ASLAP Board of Directors January 2023