UBC ANIMAL CARE COMMITTEE GUIDELINES for POLICY 017

Guidelines on Monitoring and Medical Records of Animals used for Research, Teaching and Testing

Created: May 2, 2014. Revised: April 20, 2018

PURPOSE:

The purpose of this document is to provide details on assessing animal health in different animal models. It is intended to accompany the "Policy 017 Monitoring and Medical Records of Animal used for Research, Teaching and Testing". Minimal requirements for health assessments for rodent models are included in Appendix I. A major goal of health and welfare monitoring is to be able to quickly identify "abnormal" animals and to have a clear plan of action to address the health concerns identified.

MONITORING RECOMMENDATIONS:

1. A monitoring checklist should be developed with input from all involved with animal monitoring, including the Principal Investigator (PI) and all personnel involved with the study. Input from the clinical veterinarians, post-approval monitoring (PAM) team, and members of the ACC is encouraged. This will be particularly important for non-rodent species that may have specific monitoring requirements.

2. The clinical health variables to be recorded will vary between studies. At a minimum these should capture overall health and study specific concerns.

3. For rodents, what is included in a health assessment for monitoring should be based on recommendations listed in **Appendix IA-ID.** Additional monitoring may be required for specific studies and non-rodent species.

4. Researchers should aim to complete both invasive procedures and ACC required post-procedure monitoring within normal working hours. If surgery or other major procedures are performed late in the day or on a Friday it is expected that out of hours monitoring will be done by the study team members or specifically arranged with facility staff.

5. In many studies and for many species, especially rodent species, change in weight is a helpful measure of animal health.

6. For most surgeries, animals should be assessed for pain and analgesia for up to 3 days post-operatively (for details see "UBC Animal Care Committee Guidelines -

Rodent Procedures Classifications and Analgesia Requirements"). Analgesia must be considered appropriate if the condition is known to be painful and/or the animal shows signs of pain and there is no contraindication that would make the risk of side effects outweigh the benefit. Pain relief may be required beyond the 3rd day depending on the study. Exceptions must be approved by the committee and clearly written in the protocol.

7. The actions taken by researchers when welfare concerns are identified as a result of monitoring should follow the "Policy 004 Animal Health and Welfare Concerns: Treatment and Humane Endpoints".

Appendix IA - ID: Rodent Monitoring Sheet/Record Guidelines. Minimum expected monitoring requirements for different examples of animal models.

Appendix II: References used to create monitoring sheet/record guidelines in Appendix I.

APPENDIX IC: RODENT MONITORING SHEET/RECORD GUIDELINES - These signs should be documented for experimental monitoring Monitoring sheets and humane endpoints are approved on a per protocol basis. The frequency of monitoring MUST increase with risk of deterioration and severity of clinical signs. See Appendix 2 for References

Important: More Than One Column Or Several Columns May Apply To Each Study And Additional Monitoring Requirements May Apply

Variables	Imaging with Anesthesia	Drug/chemical/biologic treatment with known species-specific toxic effects	Drug/chemical/biologic with unknown species-specific toxic effects. MTD studies	Diabetes Phenotype (e.g. NOD mice)	Diabetes-induced (e.g. STZ)
Appearance Activity Posture and Gait	During first 30-60 min following recovery from anesthesia, then every 12-24 hrs for 72 hrs or until recovered/stable or as long as repeated imaging continues.	Frequency dependent on severity and duration of clinical signs (range once daily to continuous). Monitor during expected phase of toxicity or side effects and until observed clinical signs resolve. If no lab specific experience with dose and/or route, monitor daily for at least 14 days after last dose.	After first administration monitor continuously over the first 30 minutes, then hourly for 2 hours and once in the following 4-8 hours. Daily monitoring required for at least the first two weeks. If clinical signs (Grade 3-4[2]) are noted then animals should be monitored twice daily. If potential for severe signs of toxicity (e.g. seizures, labored breathing, lethargy, pain) then hourly monitoring is recommended until risk decreases.	Every other day to weekly after DM onset (will depend on treatments).	Daily after administration of STZ or Alloxan.
Body Weight Initial baseline weight required	Post-imaging, daily until pre-imaging weight recovers or is stable.	Prior to treatment, daily for toxic drugs or weekly for non-toxic drugs until weight recovers or is stable. Non-toxic compounds and infrequent	Daily until weight recovers or is stable.	When blood or urine glucose or polyuria and polydipsia identified or starting at 10 weeks in NOD mice. Every other day to weekly after DM onset	Every other day to weekly after induction of DM (will depend on treatments).

Variables	Imaging with Anesthesia	Drug/chemical/biologic treatment with known species-specific toxic effects	Drug/chemical/biologic with unknown species-specific toxic effects. MTD studies	Diabetes Phenotype (e.g. NOD mice)	Diabetes-induced (e.g. STZ)
		administration by normal route does not require additional monitoring.		(will depend on treatments).	
Hydration	Daily for 72 hrs or until recovered/stable or as long as repeated imaging continues.	Drug specific as above in "appearance" category.	Minimum daily as above.	Every other day to weekly after DM onset (will depend on treatments).	Daily after injection.
Temperature					
Respiration		If potential respiratory effects then monitor at least once daily during risk period and when using oral gavage.	Minimum daily as above		
Elimination	If using radiation, monitor for diarrhea daily as above.	Drug specific: If potential gastrointesitnal effects then monitor daily during risk period.	Minimum daily as above.	Every other day to weekly after DM onset (will depend on treatments).	Daily after injection looking for indication of polyuria and polydipsia. Daily after onset of DM.
Neurological Signs		Drug specific: If potential neurological effects then monitor daily during risk period. Monitor for: head tilt, circling, ataxia, seizures, & altered behavior.	Minimum daily as above.		

Variables	Imaging with Anesthesia	Drug/chemical/biologic treatment with known species-specific toxic effects	Drug/chemical/biologic with unknown species-specific toxic effects. MTD studies	Diabetes Phenotype (e.g. NOD mice)	Diabetes-induced (e.g. STZ)
SKIN Incision, Wound, injection or sampling site	Injection Site: If injecting agents, such as contrast, monitor site of injection daily for 1-2 days. Monitor for inflammation, bleeding and infection.	IV route: if potential extravasation injury or repeated IV dosing, then check site immediately and ~ 10-45 min post injection and 1-2 d later for bruising/injury TOPICAL: if known skin irritant, monitor daily until resolved.	Minimum daily as above		
Tumour		Drug specific. If long term study of carcinogen monitor as per tumour guidelines.			
Other		If novel route and/or dose for the compound/drug follow recommendations for investigational drugs.	Potential toxicities should be well researched prior to study commencement. Pilot study required for substances with unpredictable effects.	Weekly blood or urine glucose when polyuria and polydipsia identified or starting at 10 weeks in NOD mice. Then daily to weekly after onset of DM (will depend on treatments).	Daily blood or urine glucose after administration of STZ or Allaxon. Daily to weekly after onset of DM (will depend on treatments).
Pain Assessment	Frequency of pain assessment depends on dosing interval for the drug chosen. See UBC Animal Care Committee Guidelines-Rodent Surgical Classifications and Analgesic Guidelines. Animals should be monitored at when the analgesia is expected to wear off (6-8h for buprenorphine, 24h for Meloxicam (Metacam) or Ketoprofen (Anafen), especially for the first 24h.				

Variables	Imaging with Anesthesia	Drug/chemical/biologic treatment with known species-specific toxic effects	Drug/chemical/biologic with unknown species-specific toxic effects. MTD studies	Diabetes Phenotype (e.g. NOD mice)	Diabetes-induced (e.g. STZ)
		Post administration & frequency appropriate for drug, if needed.	Post administration and minimum daily.		
Nursing care depends on health assessment and scientific goals of study	Heat support, food placed on bottom of cage, additional treats and gel water replacement on cage floor and /or fluid replacement (SQ fluids) until recovered/stable. Care will depend on frequency and type of imaging.	Consider humane endpoints and effects on study data instead of extending an animal's life using nursing care. Nutritional, hydration and other support may help in some cases.	Consider humane endpoints and effects on study data instead of extending an animal's life using nursing care. Nutritional, hydration and other support may help in some cases.	Consider humane endpoints and effects on study data instead of extending an animal's life using nursing care. Nutritional, hydration and other support may help in some cases. Other: Warming if hypothermic. Insulin or IP dextrose for metabolic corrections for some studies.	Consider humane endpoints and effects on study data instead of extending an animal's life using nursing care. Nutritional, hydration and other support may help in some cases. Other: Warming if hypothermic. Insulin or IP dextrose for metabolic corrections for some studies.
Humane endpoints specific to model and referenced in the literature. Ensure typical endpoints and study-specific	Typical endpoints	Typical endpoints Other: Skin necrosis at injection site or difficulty breathing post-gavage.	Typical endpoints Other: Skin necrosis at injection site or difficulty breathing post-gavage. For Toxicity or Maximum Tolerated Dose studies exceptions may be permitted.	Typical humane endpoints Other: Severe muscle weakness, inability to maintain hydration, prolonged hyperglycemia.	Typical humane endpoints Other: Severe muscle weakness, inability to maintain hydration, prolonged hyperglycemia.

Variables	Imaging with Anesthesia	Drug/chemical/biologic treatment with known species-specific toxic effects	Drug/chemical/biologic with unknown species-specific toxic effects. MTD studies	Diabetes Phenotype (e.g. NOD mice)	Diabetes-induced (e.g. STZ)
endpoints are included.					

APPENDIX II: REFERENCES – Sorted in alphabetical order by model

Colitis:

Borenshtein, D. et al, 2007. Development of fatal colitis in FVB mice infected with *Citrobacter rodentium*. *Infection and Immunity* 75(7): 3271–3281.

Ding, H. et al, 2014. Effect of homocysteine on intestinal permeability in rats with experimental colitis and it's mechanism.*Gastroenterology Report* 2(3):215-220.

Ishiguro, K. et al, 2010. Novel mouse model of colitis characterized by hapten-protein visualization. *Biotechniques*. 49:641-648.

Ostanin, D. et al, 2008. T cell transfer model of chronic colitis: concepts, considerations, and tricks of the trade. *Am J Physiol Gastrointest Liver Physiol*. 296(2): G135-G146.

Shakir, D. et al, 2013. Novel Insights on the Effect of Nicotine in a Murine Colitis Model. *The Journal of Pharmacology and Experimental Therapeutics*. 344:207-217.

Wirz, S. et al, 2007. Chemically induced mouse models of intestinal inflammation. *Nature Protocols.* 2(3): 541-546.

Diabetes:

Deeds, M.C., J.M. Anderson, D.A. Gastineau, H.J. Hiddinga, A. Jahangir, N.L. Eberhardt and Y.C. Kudva. 2011. Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation. *Laboratory Animals* 45: 131-140.

Graham, M.L., J.L. Janecek, J.A. Kittridge, B.J. Hering and H.J. Schuurman. 2011, The streptozotocin-induced diabetic Nude mouse model: differences between animals from different sources. *Comparative Medicine* 61(4): 356-360.

Hayashi, K., R. Kojima and M. Ito. 2006. Strain differences in the Diabetogenic activity of Streptozotocin in mice. *Biological and Pharmaceutical Bulletin*. 29(6): 1110-1119.

Pinheiro, L., A. Dutra de Melo, A. Andreazzi, L. Carlos de Carlos Júnior, M. Barros Costa and R. González Garcia. 2011. Protocol for insulin therapy for streptozotocin-diabetic rats based on a study of food ingestion and glycemic variation. *Scandinavian Journal of Laboratory Animal Science*. 38(2): 117-127.

Sakata, N., G. Yoshimatsu, H. Tsuchiya, S. Egawa and M. Unno. 2012. Animal models of Diabetes Mellitis for islet transplantation. *Experimental Diabetes Research* 2012: 1-11.

Drug Administration/toxicity Studies:

Boston University Guidelines on Administration of Drugs and Experimental Compounds in Mice and Rats.

http://www.bu.edu/orccommittees/iacuc/policies-and-guidelines/administration-of-drugs-and-experimental-compounds-in-mice-and-rats/

Fillman-Holliday, D and Landi, M.S., 2002. Animal Care Best Practices for Regulatory Testing. *ILAR Journal.* 49S-58S.

Guidance for Industry: Immunotoxicology Evaluation of Investigatiuonal New Drugs. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). October 2002. Pharmacology and Toxicology.

Guidance for Industry: Single Dose Acute Toxicity Testing for Pharmaceuticals. Center for Drug Evaluation and Research (CDER). August 1996.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079270.pdf

Guidance for Industry: S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Center for Drug Evaluation and Research (CDER) Centre for Biologics Evaluation and Research (CBER). May 2012. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm194490.pdf

Ji-qun, C. et al., 2005. Long-lasting antiepileptic effects of levetiracetam against epileptic seizures in the spontaneously epileptic rat (SER): differentiation of levetiracetam from conventional antiepileptic drugs. *Epilepsia.* 46(9):1362-1370.

OECD (2002). Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Human Endpoints for Experimental Animals Used in Safety Evaluation, OECD Series on Testing and Assessment, No. 19, OECD Publishing. doi: 10.1787/9789264078376-en

Parasuraman, S., 2011. Toxicological screening. *Journal of Pharmacology and Pharmacotherapy* 2(2): 74-79.

Sass, 2000. Humane endpoints and Acute Toxicity Testing. *ILAR Journal*. 41(2): 114-123.

EAE:

Care of EAE Mice UCLA website http://ora.research.ucla.edu/OARO/Pages/ARC-policies/EAE-mice.aspx

Miller, S.D., W.J. Karups and T.S. Davidson. 2007. Experimental Autoimmune Encephalomyelitis in the mouse. *Current Protocols in Immunology* Chapter Unit-15.1. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2915550/pdf/nihms190586.pdf

Olechowski, C.J., J.J. Truong and B. kerr. 2009. Neuropathic pain behaviours in a chronic-relapsing model of experimental autoimmune encephalomyelitis (EAE). Pain 141:156-164.

Stromnes, I. M. and J.M. Goverman. 2006. Active induction of experimental allergic encephalomyelitis. Nature Protocol 1 (4): 1810-1819.

Wolfensohn, S., P. Hawkins, E. Lilley, D. Anthony, C. Chambers, S. Lane, M. Lawton, H.M. Voipio and G. Woodhall. 2013. Reducing suffering in experimental autoimmune encephalomyelitis (EAE). Journal of Pharmacological and Toxicological Methods 67: 169-176.

Food Restriction:

Boston University Guidelines on Food Regulation and Restriction in Rodents

www.bu.edu/orccaommittees/iacuc/policies-and-guidelines/food-regulation-and-restriction-in-rodents/

Jensen, T.L., M.K. Kiersgaard, D.B. Sørensen and L.F. Mikkelsen 2013. Fasting mice: a review. *Lab Animal* 47: 225.

Rowland, Neil E. 2007. Food or Fluid Restriction in Common Laboratory Animals: Balancing Welfare Considerations with Scientific Inquiry. *Comparative Medicine* 57(2): 149-160.

Imaging:

Baumans, V. 2010. The Laboratory Mouse. In The UFAW Handbook on The Care and management of Laboratory and Other Research Animals. Eds. Hubrecht and Kirkwood 2010. Wiley-Blackwell, Oxford, UK.

Duke, T. and J. Henke 2008. Control of blood pressure under anesthesia In Essential Facts of Blood Pressure in Dogs and Cats. Eds Egner, B. and A. Carr VBS, VetVerlag, Germany.

Fairchild, G.A. 1972. Measurement of Respiratory Volume for Virus Retention Studies in Mice, *Applied Microbiology* 24 (5): 812-818.

Hoyt, R.F. Jr., Hawkins, J.V., St Clair, M.B. and M.J. Kennett 2007. Mouse Lung Measurements In The Mouse in Biomedical Research: Normative Biology, Husbandry, and Models. Eds. Fox, J.G., Barthold, S.W., Davisson, M.T., Newcomer, C.E., Quimby, F.W. and A.L. Smith 2007 Academic Press, New York.

Jacoby, R.O., Fox, J.G. and M. Davisson 2002. Biology and Diseases of Mice. In Laboratory Animal Medicine 2nd Edition. Eds. Fox J.G., Anderson, L.C., Loew, F.M. and F.W. Quimby. Academic Press, San Diego.

Khalil, M.M., J.L. Tremoleda, T.B. Bayonny and W. Gsell. 2011. Molecular SPECT imaging: an overview. *International Journal of Molecular Imaging*. Article ID 796025, 15 pages.

Kohn, D.F. and C.B. Clifford 2002. Biology and Diseases of Rat. In Laboratory Animal Medicine 2nd Edition. Eds. Fox J.G., Anderson, L.C., Loew, F.M. and F.W. Quimby. Academic Press, San Diego.

Koolhaas, J. M. 2010. The Laboratory Rat. In The UFAW Handbook on The Care and management of Laboratory and Other Research Animals. Eds. Hubrecht and Kirkwood 2010. Wiley-Blackwell, Oxford, UK.

Strohl, P., Thomas, A.J., St. Jean, P., Schlenker, E.H., Koletsky, R.J. and N.J. Schork 1997. Ventilation and metabolism among rat strains. J. *Applied Physiology* 82:317-323.

Tremoleda, J.L., A. Kerton and W. Gsell. 2012. Anaesthesia and physiological monitoring during in vivo imaging of laboratory rodents: considerations on experimental outcomes and animal welfare. *EJNMMI Research* 12: 44 pages.

Tremoleda, J.L., M. Khalil, L.L. Gompels, M. Wylezinska-Arridge, T. Vincent and W. Gsell. 2011. Imaging technologies for preclinical models of bone and joint disorders. *EJNMMI Research* 1: 14 pages.

Infectious Disease:

Franco et al. How “Humane” is Your Endpoint? Refining the Science-Driven approach for Termination of Animal Studies of Chronic Infection. PLOS pathogens.

http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1002399

Olfert et al. Humane Endpoints for Infectious Disease Animal Models. *ILAR Journal*. 2000. 41(2): 99-104.

Hakenson et al. 2013Weight loss and Reduced Body Temperature Determine Humane Endpoints in a Mouse Model of Ocular Herpesvirus Infection. 2013. *JAALAS*. 52(2):277-285.

Irradition:

Boston University IACUC Policy on Irradiation of Rodents

WWW.bu.edu/orccomittee/iacuc/policies-and-guidelines/irradiation-of-rodents/

Nunamaker et al. 2013. Predictive Observation-Based Endpoint Criteria for Mice Receiving Total Body Irradiation. *Comparative Medicine* 63(4): 313-322.

Nunamaker et al. 2013. Endpoint Refinement for Total Body Irradiation of C57BL/6 Mice. *Comparative Medicine* 63(1): 22-28.

Longevity/Aging:

Ray et al., 2010. Identification of Markers for Imminent Death in Mice used in Longevity and Aging Research. *Journal of the American Association for Laboratory Animal Science.* 49(3): 282-288.

Heiderstadt, K and Kennett, M.J., 2011. IACUC Issues Related to Animal Models of Aging. *ILAR Journal*. 52(1): 106-109.

NIH Office of Animal Care and Use: Guidelines for Endpoints in Animal Study Proposals. Revised 2013. http://oacu.od.nih.gov/ARAC/documents/ASP_Endpoints.pdf

Pettan-Brewer, C. and P.M. Treuting 2011. Practical pathology of aging mice. *Pathology of aging and age-related diseases*. 1.

Spindler, S.R. 2012. Review of the literature and suggestions for the design of rodent survival studies for the identification of compounds that increase health and life span. *Age.* 34:111-120.

Shimokawa, I. et al, 2003. Lifespan extension by reduction of the growth hormone-insulin-like growth factor-1 axis: relation to caloric restriction. *The FASEB Journal.* April:

Tumors:

Jensen, M.M., J. T. Jørgensen, T. Binderup and A. Kjær. 2008. Tumor volume in subcutaneous mouse xenografts measured by microCT is more accurate and reproducible than determined by 18F-FDG-microPET or external caliper. *BMC Medical Imaging* 8:16-24.

Morris et al., 2002. The international Symposium on Regulatory Testing and Animal Welfare: Recommendations on Best Scientific Practices for Animal Care in Regulatory Toxicology. *ILAR Journal*. S123-125.

Paster, E.V., K.A. Villines and D.L. Hickman. 2009. Endpoints for mouse abdominal tumor models: refinement of current criteria. *Comparative Medicine* 48 (3): 234-241.

Schuh, J.C.L. 2004. Trials, tribulations, and trends in tumor modeling in mice. Toxicologic *Patholog*y. 32: 53-66.

Tomayko, M.M. and C.P. Reynolds. 1989. Determination of subcutaneous tumor size in athymic (nude) mice. *Cancer Chemotherapy and Pharmacology*. 24: 148-154.

Ullman-Culleré M.H. and C.J. Foltz. 1999. Body Condition Scoring: A Rapid and Accurate Method for Assessing Health Status in Mice. *Laboratory Animal Science* 49 (3): 319-323.

Workman, P., E.O. Aboagye, F. Balkwill, A.Balmain, G. Bruder, D.J. Chaplin, J.A. Double, J. Everitt, D.A.H. Farningham, M.J. Glennie, L.R. Kelland, V. Robinson, I.J. Stratford, G.M. Tozer, S. Watson, S.R. Wedge, S.A. Eccles. 2010. Guidelines for the welfare and use of animals in cancer research. *British Journal of Cancer* 102: 1555-1577.

Workman , P. 1998. United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Guidelines for the Welfare of Animals in Experimental Neoplasia (Second Edition). *British Journal of Cancer* 77 (1): 1-10.

Surgery:

ACLAM (2006) Guidelines for the Assessment and Management of Pain in Rodents and Rabbits.

Flecknell (2009) Laboratory Animal Anaesthesia 3rd Edition.