Responsibilities of Principal Investigators Maintaining Mutant Strains of Mice (Spontaneous Mutants, Generation of Transgenic or Gene Knockout Mice)

The phenotypes of mice that occur spontaneously or by generation of transgenic and knockout technologies are often times unpredictable. The changes, induced by the genetic alteration of the host genome, can vary from mild to debilitating phenotypes in animals requiring investigators and animal care staff to devise effective strategies for monitoring and managing these colonies. The following guidelines are intended for use in establishing and caring for these mice.

I. Principal investigators proposing to "add" a gene to the genome via generation of transgenic mice or to "alter or delete" an existing gene via homologous recombination should describe in advance expected "mutant" phenotypes of the animals and possible affects on the animals well-being.

II. The Recombinant DNA Form should be attached to the protocol, if viral DNA or retroviral vectors are being used. Additional information to assure the safety of these agents may be required by the NCI-Frederick Environmental Health and Safety Program and/or the NCI-Frederick ACUC.

III. Since altered phenotypes often results from the expression of new genes or deletion of an existing gene within the genome, it is essential that close examinations be conducted on the condition of these animals.

IV. When there is a potential for animal pain, distress, or suffering, investigators need to outline clearly the research objectives and procedures for assessing animal well-being. The investigator needs to define appropriate experimental endpoints that allow for an end to the study in advance of morbundity. The NCI-Frederick ACUC requires that:

- When abnormalities are observed (see SOP 3.020) the facility manager will contact the investigator and the attending veterinarian, if a new stock or strain is producing animals that are unable to eat, drink, or fulfill other normal behavioral and physiological needs. Animals should be adequately identified for phenotype and any interventions that might be required. If accommodations are not possible to relieve pain and distress the animal will be humanely euthanized.

- Once a specific phenotype has been characterized, criteria can be established to assure the animal's well-being. The identification of new phenotypes in genetically altered strains/stocks does not relieve the principal investigator, animal care, technical, or veterinary staff of responsibility for providing continued monitoring, evaluation, and support to these animals.

- In circumstances involving declining health status, morbundity, or unrelieved pain and discomfort, every attempt will be made to reach consensus with the principal investigator bearing experimental endpoints in mind. However, the final analysis and discharging of the NCI-Frederick's

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animal care and use regulatory responsibility rests with the attending veterinarian.

V. Anytime that an animal exhibits an adverse change in health status as a result of a genetic alteration, the *Deleterious Phenotype Reporting Form* (see attached) must be completed by animal facility technical personnel or the facility manager. After review by the investigator, the form is submitted to the ACUC for review.

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