I. PURPOSE

To establish guidelines for the management of an animal room/suite that is confirmed for mouse hepatitis virus (MHV); and to establish guidelines for the depopulation and subsequent repopulation of an animal room/suite resulting from an MHV outbreak.

II. POLICY STATEMENT

The School of Medicine does not have a prior formal policy for active management of infectious disease outbreaks in research animal facilities. This serves as the official school policy for responding to an MHV infection and mitigating future outbreaks.

III. WHO SHOULD KNOW THIS POLICY?

- Dean
- Vice Dean for Research and Research Training
- School of Medicine Animal Research Committee (SOM-ARC)
- Faculty and lab personnel engaged in animal research
- University Laboratory Animal Research (ULAR) Staff
- IACUC Chair

IV. POLICY AND PROCEDURES

Detection of MHV Infection and Notification

The detection of MHV infection within SOM animal facilities may occur by several means including, but not limited to:

- Notification by an external entity of the shipment of infected animals
- Diagnostic results from individual animals within the colony
- The results of diagnostic tests performed on sentinel animals

In this regard, it is expected that ULAR will maintain a rigorous sentinel program to detect such agents. The SOM-ARC will be notified by ULAR of a suspected or confirmed MHV agent when either:

- An outside entity provides preliminary notification of infection.
• There is a diagnostic detection (serology and/or PCR) of MHV in the existing colony.

Notification to the SOM-ARC should occur via the committee chair within 24 hours of either of these events. Within 48 hours of this time, ULAR Diagnostic Services will present a comprehensive Outbreak Management Plan (OMP) for the facility to the SOM-ARC. The OMP will be revised based on the results of each testing phase.

**Management of Infected Rooms**

**Phase One:**

1. The positive room will immediately be placed on quarantine in accordance with Policy Number RA-ANML-002: Quarantine of Rodents Due to Infectious Disease of Outbreak in School of Medicine Animal Facilities. If the room is within BRB, the affected BRB suite will be placed on quarantine.

2. ULAR will alert the SOM-ARC and all faculty who have mice in the affected room/suite/facility at the same time the room/suite/facility is placed under quarantine. Within the same week a meeting will be held with all affected faculty to present and discuss the OMP.

3. After notifying the faculty, any cages containing sero-positive mouse/mice will be either: (a) promptly euthanized by the faculty; (b) marked by the faculty for euthanasia by ULAR staff. All sero-positive cages will then be placed in bagged containers and removed from the room(s) as soon as possible by ULAR staff. Whenever possible these events should occur with in 24* hours after notification.

4. All cages in the infected room will have blood drawn for appropriate diagnostic testing and will be mailed to ULAR-approved diagnostic vendors as soon as possible after notification (within 48* hours whenever possible). ULAR Diagnostic Services will supervise these events. It is expected that individual laboratories will work in concert with and under the supervision of ULAR Diagnostic Services to accomplish this task. By standard practice ULAR Diagnostic Services and other trained ULAR personnel will conduct these bleedings. However, if the magnitude of the outbreak or other events prohibits this, Diagnostic Services will identify individual laboratories to assist in the process (as specified in the OMP). Whether scientists or ULAR staff bleed the mice, each cage and serum must be clearly identified so that positive results may be traced unequivocally to specific cages.

5. In accordance with the guidelines for Policy Number RA-ANML-002: Quarantine of Rodents due to Infectious Disease Outbreak in School of Medicine Animal Facilities: (a) scientists and ULAR staff will avoid relocating cages within quarantined rooms; (b) cages in quarantine rooms will not be moved to
other rooms; and (c) no new arrivals of mice from approved vendors will be approved to the affected room(s). New shipments of mice that had already been ordered prior to the quarantine will be considered on a case-by-case basis.

6. All sentinels in adjacent rooms will have blood drawn by ULAR staff as soon as possible, as specified in the OMP.

7. The results of all tests will be forwarded to the SOM-ARC, and affected faculty, on the same day that the results arrive.

Phase Two:

1. If no other positive cages are detected from Phase One tests, the testing will be repeated. The timing for this second bleed will be no sooner than 14 days (for MHV) after the first bleed to allow time for seroconversion. Two sequential fully negative tests are considered evidence of clearance.

2. If any other positive cages are detected, affected faculty will be notified, and these animals will be euthanized. Cages will then be removed from the affected room(s) and placed in bagged containers by ULAR staff within 24* hours, as stated in Phase One.

3. All cages in the infected rooms will be retested as soon as possible, but no earlier than 14 days (for MHV) after the initial bleed. As noted in Phase One, it is expected that individual laboratories will work in concert with and under the direction of ULAR veterinarians to accomplish this task.

4. Faculty having mice in more than one room and/or suite will be required to test all of their cages in other rooms/facilities, under ULAR supervision. In addition, an acceptable pattern of room entry order will be developed by ULAR and communicated to these faculty to ensure that scientists are entering rooms in a “clean-to-dirty” order each day.

5. For rooms in BRB, 25% of the cages in the remainder of the suite will be randomly tested as soon as possible; the timeline for this will be outlined in the OMP. For rooms outside of BRB, 25% of cages will be randomly tested in all other rooms (all facilities) that house cages of investigators from the primary infection site.

6. The results of all tests will be forwarded to the SOM-ARC, and affected faculty, on the same day that results arrive.

7. The SOM-ARC Chair, in consultation with the ULAR Director for Diagnostic Services, will be responsible for reviewing the status of the infection and
quarantine with the SOM-ARC. ULAR and the SOM-ARC will determine further actions, or modifications to the OMP required to ensure infection containment and eradication.

Phase Three:

1. If the results of Phase Two testing show that there are still positive animals (evidence of a spreading infection), the room and/or suite will be depopulated and essential mice relocated to another facility or entity, as determined by the SOM-ARC. Essential mice are defined as unique strains that cannot be purchased or re-derived from another source, or ongoing experiments that are not possible to repeat in a reasonable time frame. Exceptions to this policy will be considered by the SOM-ARC on a case-by-case basis if Phase Two results indicate that the vast majority of infected animals have been eliminated. In this instance one additional test/cull phase may be permitted.

2. The SOM-ARC and ULAR will jointly convene a meeting of all affected faculty to communicate the depopulation plan, including timelines, within 2-3 days of receiving results from Phase Two bleeding.

3. Investigators who have mice in a room that is scheduled for depopulation will identify essential mice for relocation and submit a request to the SOM-ARC which documents:
   - A description of all essential strains
   - Estimated number of animals per strain
   - Estimated number of required breeding and non-breeding isolators
   - Brief justification for why individual strains need to be preserved

4. The SOM-ARC will evaluate individual faculty requests and forward decisions to the faculty within 48* hours.

5. If an alternate, on-campus facility is not available for relocation, the SOM-ARC will identify an external vendor. Faculty must then obtain a vendor cost estimate, and submit this to the SOM-ARC for final approval. Faculty will work with the SOM-ARC to insure that appropriate Risk Management invoices are completed prior to shipment of any animals. The full SOM procedure for this process is included as Attachment 1.

6. Upon receipt of full SOM-ARC approval, ULAR will coordinate the evacuation of the infected room/suite/facility and the transfer of essential mice to another location/vendor within a timeline identified in Phase Three of the OMP. The OMP will precisely state the deadline by which all animals must be removed. After this deadline ULAR staff will euthanize any remaining animals.
7. ULAR will schedule the room decontamination, which will occur within 1 business day of full depopulation, and will then coordinate the re-introduction of mice to the room.

8. Following depopulation, sentinels in the other affected rooms (suite or facility as noted in Phase Two) will be tested by no later than 3 weeks for potential seroconversion. If all sentinel tests are negative, the quarantine will be immediately lifted.

* Exceptions to this timeline will be identified in the outbreak management plan developed by ULAR in concert with the SOM-ARC.

V. CONTACTS

Vice Dean, Research and Research Training, School of Medicine
   Phone: 215.898.2874
   Fax: 215.573.7945

Director, University Laboratory Animal Resources
   Phone: 215.898.2433/4
   Fax: 215.573.9999

Chair, Institutional Animal Care and Use Committee
   Phone: 215.898.2615
   Fax: 215.573.9438

VI. ATTACHMENTS

Attachment 1: SOM MHV Reimbursement Process

Attachment 2: Services Available from the TCMF Core for Preservation and Re-derivation of Mouse Lines Under Current Quarantine Rules

Attachment 3: ULAR Request to Send Rodents to other Institutions

Attachment 4: Charles River Laboratories Model Information Form—Transgenic Services

Supersedes: NONE—New Policy

APPROVED:

Vice Dean, Research and Research Training, SOM Date
MHV Reimbursement Process

1. Investigators must receive SOM approval PRIOR to shipping mice to external vendors.

2. An investigator’s needs for housing or re-deriving mice during de-population may be met either internally through the Transgenic and Chimeric Mouse Facility (cryopreservation and re-derivation) or externally through a vendor such as Charles River. A cost estimate and SOM approval are required for both internal and external services.

3. Submit request to the Vice Dean for Research and Research Training via Nam Narain (narain@mail.med.upenn.edu)

4. Request should include the following:
   a. Letter addressed to Dr. Gaulton explaining the request and its impact on research, including:
      - A description of all essential strains. (Essential mice are defined as unique strains that cannot be purchased or re-derived from another source, or ongoing experiments that are not possible to repeat in a reasonable time frame.)
      - Estimated number of animals per strain
      - Estimated number of breeding and non-breeding isolators
      - Brief justification for why individual strains need to be preserved
   b. Cost estimate for re-deriving and/or freezing the mice
      - Contact Information for Transgenic and Chimeric Mouse Facility:
        http://www.med.upenn.edu/genetics/core-facs/tcmf/
        Kathleen A. Thompson
        Research Specialist
        Tel: 215/573-3023; 215/746-6392
        Email: kthompson@mail.med.upenn.edu
        Attached is a description of cryopreservation and re-derivation services available from the Transgenic and Chimeric Mouse Facility.
      - Contact Information for Charles Rivers:
        Chris Aitken
        Product Coordinator, Transgenic Services
        Charles River Laboratories
        Tel: 978-658-6000 Ext. 1684
        Fax: 978-658-6974
        caitken@criver.com
- Model information forms for transgenic services for the Charles River Diagnostic Laboratory may be found at http://www.criver.com/SRM/tgs/pdf/TG_FM_ModelInformationForm.pdf
- Request to Send Rodents to Other Institutions form (ULAR) can be found at: http://www.ular.upenn.edu/forms/Ship_Rodents_to_Institutions_Form.pdf
- Contact Information for Jackson Laboratory:
The Jackson Laboratory
600 Main Street
Bar Harbor, ME 04609
Contact: Ms. Kathy Norwood
Telephone: 207-288-6000
- If you prefer to use another commercial vendor, please let us know.

Contact person at Penn (ULAR) for animal shipments out is Ed Mack (edmack@pobox.upenn.edu).

c. Completed Incident Report Form, Office of Risk Management, located at http://www.finance.upenn.edu/riskmgmt/propins.html. You can reach the actual form by clicking on item#2, where it says attached form. Please send the completed Incident Report Form to Nam Narain. Please leave the account information section blank. Nam Narain will contact your Business Administrator (BA) with account information.

5. Once the request has been reviewed and approved at SOM level (2 business days,) it is then forwarded to Risk Management. As soon as Risk Management has approved the request (5-7 business days), a SOM designated account will be provided to your BA, along with the approved amount that can be charged to this account.

6. If initial estimate of costs is likely to rise, please submit explanation and budget for additional expenses for approval.
SERVICES AVAILABLE FROM THE TCMF CORE FOR PRESERVATION AND RE-DERIVATION OF MOUSE LINES UNDER CURRENT QUARANTINE RULES

Date: October 10, 2004
From: The Transgenic and Chimeric Mouse Facility (TCMJ)

The following services are available from the TCMF under the current quarantine rules. These services will allow users in the Medical School to store valuable lines in liquid N2 for future use. These methods will help insure against permanent loss of lines due to disease and mishap and all the re-establishment of infected lines.

1. Sperm Cryopreservation. This is the easiest approach. The user isolates the epididymis from 3 healthy males and brings it to the core. The sperm are isolated and frozen. The lines can be brought back subsequently via IVF.

   For cryopreservation at least 3-5 males between the ages of 8 weeks and 6 months are optimal. Since animals cannot be currently transferred to the CRB, the isolation must be done by the user in his/her own facility. This requires hands-on training of lab personnel for the epididymis harvest. Media is supplied by TCMF to all labs. 5 straws of sperm per male are frozen. QC is done by pulling one straw per line and performing IVF to measure two-cell development. Subsequent re-derivation requires IVF (see 3., below).

2. Embryo Cryopreservation. This takes a bit more work on the part of the user as the mating to generate the embryos and the subsequent isolation of the oviducts must be carried out in his/her own facility due to the current quarantine rules.

   Specifically, this requires hands-on training of lab personnel in ip hormone injection and oviduct harvest. All media and hormones are supplied by the Core facility well as the actual training. The lab would be responsible for two hormone injections 48 hrs apart between the hours of 12PM and 2PM of 3-week old females. Once the second hormone injection is complete, the female mice are placed with single caged males and left alone for 2.5 days. On the morning of harvest, females are sacrificed, organs removed and someone who has not been near the actual animals delivers the organs to the Core in a doubled Petri dish. Approximately 150 embryos in a total of 10 straws are frozen. QC is done once cycle is complete by removing one straw and allowing sample to go to blastocysts. These embryos can also be cultured in the Core to the blastocyst stage and re-implanted for re-derivation of the line. The transplanted pseudo-pregnant recipients are then transferred to Levy for gestation and quarantine monitoring. ULAR diagnostics must be contacted and space within Levy quarantine cleared before any date will be set.
3. Embryo Re-derivation by IVF. This is another approach to re-derivation. Due to present quarantine, re-derivation cannot be accomplished by the routine method of carrying on matings in the Core, because the Core cannot receive mice from other facilities on campus. However re-derivation can be done via IVF.

The epididymis of the donor male is harvested by the user (as in 1., above), delivered to the core and the sperm is used for IVF of wt eggs. The eggs will have to be harvested in the Core from vendor females (if ULAR allows such importation). The transplanted pseudo-pregnant recipients are then transferred to Levy for gestation and quarantine monitoring. ULAR diagnostics must be contacted and space within Levy quarantine cleared before any date will be set.

Transgenic and Chimeric Mouse Facility
http://www.med.upenn.edu/ulrgenetics/core-facilities/tcrnf/

For questions about cryopreservation or re-derivation services, please contact:

Kathleen A. Thompson
Research Specialist
Tel: 215/573-3023; 215/746-6392
Email: kthompsomaiLmed.upenn.edu
Attachment 3: Request to Send Rodents to Other Institutions

ULAR Memorandum

TO: University of Pennsylvania Investigators

FROM: Laboratory Animal Diagnostic Services & Office of Procurement
                    University Laboratory Animal Resources
                    Diagnostic Services
                    Medical School Mailroom
                    MC 6014
                    Phone: 215.573.4546
                    Fax: 573-9998

RE: Procedures for Shipping Rodents to Other Institutions

To initiate the process of sending rodents to colleagues at other institutions, please provide the information requested in this packet. Return the completed 2-page information sheet entitled “Request to Send Rodents to Other Institutions” to ULAR Diagnostic Services at least 2 weeks prior to the requested delivery date. Please note that the embossed original must be received to complete the order.

Typically, the receiving institution will require HEALTH REPORTS and a description of the rodent sentinel health surveillance program to determine if rodents are acceptable for receipt from the University of Pennsylvania. This is considered standard procedure and the information will be faxed to the veterinarian or animal resources contact person designated on the information sheets. Following review of this information, the receiving institution will act to accept, reject or request further information. Once animals are accepted for delivery, regulations require that a HEALTH CERTIFICATE accompany the animals during transit. To facilitate the shipping process, it is the investigator’s responsibility to segregate the designated rodents for shipment.

International shipments may require the signature of an USDA-accredited veterinarian which requires special arrangements by ULAR. It is the investigator’s responsibility to determine if this certification is necessary.

As per University policy, the shipment of any animal to another destination is governed by a Material Transfer Agreement (MTA) prepared by the Center for Technology Transfer (CTT). The MTA is a legally binding contract restricting the use of the animals to the recipient investigator and limits the University’s liability in case of a future lawsuit. When your application is received by ULAR, the relevant sections will be forwarded to the CTT which will then initiate an MTA and contact the receiving institution. Questions regarding this process should be directed to Dr. Avijit Roy in the CTT at 215-573-4505.
ULAR coordinates all shipping arrangements through a commercial carrier, Frame’s Animal Transportation Service. Special arrangements using other commercial transport maybe made on a case-by-case basis. Once transport arrangements have been finalized, you will be notified of the date and time of packing. You are encouraged to be present when the animals are prepared for shipping. There is a processing fee incurred, in addition to the direct costs of the shipment, which is greater when a carrier other than Frame’s Animal Transportation Service is utilized. (Fees are published in the annual ULAR price list or may be obtained from the Procurement Office).

Shipping crates are obtained which may be subdivided into individual compartments. Each compartment will be provided with ample food and water kits. It is the investigator’s responsibility to inform ULAR how the animals are to be divided for shipping, i.e., separated by gender, age, relatedness; number per compartment. Ideally, rodents are placed in separate cages that represent individual compartments in a crate and labeled as indicated previously.

Inquiries regarding this process may be directed to ULAR Diagnostic Laboratory Services.
REQUEST TO SEND RODENTS TO OTHER INSTITUTIONS

DATE: _______________________

Coordination of the shipping process typically requires 2 or more weeks; please plan accordingly. When completed, return this form to ULAR Diagnostic Services, Medical School Mailroom; MC 6014; or fax to (215) 573-9998. (NOTE: Embossed original must be received to process the order).

UNIVERSITY OF PENNSYLVANIA INVESTIGATOR INFORMATION
Principal Investigator ___________________ Dept __________________________
Campus address ____________________________
Phone ___________________ FAX ___________ email ________________________
Contact Person (if different from P1) ____________________________
Phone ___________________ FAX ___________ email ________________________
IACUC Protocol # ______________________________ (An active protocol is required)

INSTITUTION TO WHICH ANIMALS ARE BEING SENT
Principal Investigator ___________________ Dept __________________________
Institution ______________________________
Phone ___________________ FAX ___________ email ________________________
Contact Person (if different from PI) ____________________________
Phone ___________________ FAX ___________ email ________________________
Shipping coordinator ______________________________
Please provide contact info if not previously listed:
Phone ___________________ FAX ___________ email ________________________
Addressee and exact address-to be placed on shipping container:


VETERINARIAN AT INSTITUTION TO WHICH ANIMALS ARE BEING SENT
Veterinarian ______________________________
Phone ___________________ FAX ___________ email ________________________
Animal Resources Contact Person (if different from veterinarian
Phone ___________________ FAX ___________ email ________________________

INFORMATION REGARDING ANIMALS TO BE SHIPPED
Which of the following best describes the animal(s) to be shipped:

1. Transgenic, identify the transgene __________________ background strain __________
2. Knockout, what gene is mutated? __________ background strain __________

REQUEST TO SEND RODENTS TO OTHER INSTITUTIONS
3. Spontaneous mutation
Designation ___________________
4. Other (please describe)
Are animals immune competent? ______ Coat color______ Number of animals:
Male _______ Female ___________

ADDITIONAL ANIMALS TO BE SHIPPED (wildtype, negative controls)

<table>
<thead>
<tr>
<th>Strain/Genotype</th>
<th>Coat Color</th>
<th>Gender</th>
<th>Quantity</th>
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UNIVERSITY OF PENNSYLVANIA INVESTIGATOR

A health certificate must accompany live-animal shipments which necessitates a clinical examination by ULAR.
For shipments originating from ULAR-managed facilities, place a blue acetate overlay, available from husbandry supervisors, over the card.
Check here to indicate that this has been completed: ________
Total # of cages marked: ________
Provide any specific packing instructions (e.g., separate by gender, # mice/compartment, special requirements)

________________________________________________________________________
________________________________________________________________________

A patent application has been, or will be, filed for any strain(s) for shipment ______ If yes, contact the Center for Technology Transfer at 215-573-4505 to prepare a Material Transfer Agreement.

BILLING INFORMATION
Costs will be incurred by (Name of individual)

Billing number for administrative processing- fee-and any shipping costs incurred:
______ - ______ - ______-5234

AUTHORIZATION SIGNATURE
Principal Investigator or Authorized Individual ___________________________
Departmental Business Administrator ________________________________
Business Administrator’s email Address ______________________________
Business Administrator’s Embossment (required for processing):
Attachment 4: Model Information Form—Transgenic Services

- Model information forms for transgenic services for the Charles River Diagnostic Laboratory may be found at