University of Pennsylvania School of Medicine Policy and Procedure Manual

MANAGEMENT OF MHV- and EDIM VIRUS-INFECTED ROOMS/SUITES IN SOM ANIMAL FACILITIES

RESEARCH ADMINISTRATION Policy Number: RA-ANML-001.1 Date Approved: December 22, 2010

I. PURPOSE

To establish guidelines for the management of an animal room/suite that is confirmed to have a viral disease outbreak (mouse hepatitis virus [MHV], epizootic diarrhea of infant mice [EDIM] virus); and to establish guidelines for the management (e.g., test-and-cull or depopulation and subsequent repopulation) of an animal room/suite resulting from a viral disease outbreak.

II. POLICY STATEMENT

A policy for the management of an animal room/suite that is confirmed to have a viral disease outbreak is essential to minimize the risk of rodent infectious disease transmission in the School of Medicine (SOM) rodent housing facilities. This policy serves as the official SOM position for the management of an animal room/suite that is confirmed to have an MHV or EDIM disease outbreak and supersedes Policy Number RA-ANML-001: Management of MHV-Infected Rooms/Suites in SOM Animal Facilities. The policy has been expanded to include the EDIM virus and to reflect current infectious disease management practices.

III. WHO SHOULD KNOW THIS POLICY?

- Executive Vice Dean and Chief Scientific Officer and staff
- Assistant Dean for Animal Research
- School of Medicine Animal Research Committee (SOM-ARC)
- Associate Dean of Research, School of Veterinary Medicine
- Faculty and lab personnel engaged in animal research
- University Laboratory Animal Research (ULAR) Staff
- IACUC Chair and staff

IV. POLICY AND PROCEDURES

Detection of Virus Infection and Notification

The detection of an excluded virus 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

Policy No. RA-ANML-001 Page 2 of 15

ULAR Diagnostic Services will provide phone and/or email notification of a presumptive viral disease agent in an existing colony to the SOM-ARC Chair immediately (within 24 hours) upon receipt of initial results or notification. A general announcement will be made once an unexpected positive result has been confirmed by a different test method and/or a different testing laboratory. In this regard, it is expected that ULAR will maintain a rigorous sentinel program to detect such agents. The SOM-ARC Chair will also be notified immediately (within 24 hours) following confirmation of the preliminary finding of virus detection by serology and/or PCR. If the result is based on serologic testing, confirmation will be sought by using a different test method and/or submission of the sample to a different laboratory. In most cases, cage mates will be sampled and tested as well.

Email notification of the SOM-ARC will occur via the committee Chair within 24 hours of confirmed infection. Within 72 hours of confirming infection, ULAR Diagnostic Services will present a comprehensive Outbreak Management Plan (OMP) for the facility to the User Group (or a subset thereof) for the facility. 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 the BRB or Hill Pavilion vivaria, the affected suite will be placed on quarantine.
- 2. Prior to the general announcement of quarantine, ULAR Diagnostic Services will contact the facility manager and/or supervisor to request that the room/suite locks be changed and will also contact the Associate Dean for Research for the Veterinary School to give notification of an outbreak. In addition, ULAR Diagnostic Services will then send an e-mail to the SOM-ARC Chair, the user group chair and all faculty (as well as their lab contacts) who have mice in the affected room/suite/facility at the same time the room/suite/facility is placed on quarantine. That e-mail will request that recipients communicate to their on-campus collaborators that a viral disease outbreak has been detected. Within the same week, preferably within 72 hours, a meeting will be held with all faculty (and their lab staff) who have animals in the affected room/suite to present and discuss the OMP.
- 3. Whenever possible, one individual from each laboratory will be identified to have sole or primary room access. ULAR staff may request the assistance of these individuals in manipulating or sampling infected mice. To avoid disruption of the screening process, mice should not be removed from cages during quarantine without written approval from the Associate Director, ULAR Diagnostic Services, has been sent to the investigator and the facility manager and supervisor.
- 4. One mouse from each colony cage in the quarantined room will have blood drawn for appropriate diagnostic testing by the ULAR Diagnostic Serology Laboratory (or serum will be express-shipped to a ULAR-approved diagnostic laboratory) within 48 hours (or as soon as possible) after infection has

Policy No. RA-ANML-001

Page 3 of 15

- been confirmed. If there are known immunodeficient mice housed in the room(s), fresh fecal pellets will be collected and frozen at -80C for shipping to a diagnostic laboratory for RT-PCR. ULAR Diagnostic Services will be responsible for these activities. Each cage and blood or fecal sample must be clearly identified so that positive results may be traced unequivocally to specific cages. ULAR Diagnostic Services maintains pre-printed labels for this purpose.
- 5. Any cages containing positive mice will be marked for euthanasia by ULAR staff. If mice belonging to investigators must be euthanized, those individuals will be notified at least 48 hours prior to euthanasia. However, the animals will not be euthanized without a member of the lab being notified. The PI is notified first and, if no response is received, the lab manager or contact person listed on the cage card is contacted. All cages that contained seropositive or PCR-positive animals will then be bagged for autoclaving and removed from the room(s) as soon as possible by ULAR staff. Whenever possible these events should occur within 24 hours of documenting that cages contain(ed) infected mice.
- 6. 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 their staff and ULAR staff will make every effort to avoid relocating cages within quarantined rooms (shelf-to-shelf; rack-to-rack); (b) under no circumstances will cages in quarantined room(s) be moved to other rooms in the facility or any other campus facility; and (c) no new arrivals of mice from approved vendors or rodents released from Levy quarantine will be approved to enter the affected room(s)/suite(s). New shipments of mice that had already been ordered prior to the quarantine will be considered on a case-by-case basis. Rather than assigning affected investigators housing space in alternate locations, they will be encouraged to use mice acutely if possible. The ULAR Procurement staff is informed of the quarantine status at the same time as the research staff and will utilize the established SOP for informing vendors of cancelled orders.
- 7. Research staff having animals in the virus-positive quarantined room/suite/facility will be identified and ULAR Diagnostic Services will determine, through Polaris, whether these investigators have rodents housed in other rooms/suites/facilities. "Collateral" testing will be performed as soon as possible to determine whether there has been transmission to rodents in other areas.
- 8. In outbreaks involving rooms within suites (i.e., BRB or Hill Pavilion vivaria), all sentinels housed in other rooms within the suite(s) will be tested and a randomly selected subset of colony animals may be tested as well.
- 9. The results of all tests will be forwarded by email to the SOM-ARC Chair and all investigators housing mice in the affected facility on the same day that the results are available.

Policy No. RA-ANML-001 Page 4 of 15

Phase Two:

- If fewer than 4% of the cages in the room are positive, a "test-and-cull" approach will be adopted with the second set of samples collected approximately 21 days after the first. If more than 4% of the cages in the room are positive, the room will be de-populated by any of several methods that may include: (a) culling (euthanasia) of non-essential mice; (b) removal of essential mice via shipping to an offcampus site for holding and additional testing; (c) shipping unique animals to an off-campus location for rederivation.
- 2. All mice in room(s) having fewer than 4% of cages positive will be retested as soon as possible, but no earlier than 21 days after the initial bleed. This interval maximizes the likelihood that seroconversion will occur due to active infection in the room population.
- 3. If any other positive animals are detected, investigators will be notified, and these animals will be euthanized by ULAR staff. Cages will be placed in autoclave bags and removed from the affected room(s) for autoclaving by ULAR staff within 24 hours, as stated in Phase One.
- 4. If no other positive mice are detected, the testing will be repeated. The timing for the third sampling will be at least 21 days after the second bleed to allow time for seroconversion. If the second and third tests are uniformly 100% negative, this will be considered evidence of viral clearance from the population.
- 5. The proportion of cages to be screened in any given room/suite/facility (identified as collateral to the affected room) will be communicated by ULAR Diagnostic Services. The use of change stations/hoods in rodent rooms has dramatically reduced the amount of transmission within and from affected rooms. For this reason, ULAR Diagnostic Services staff has been routinely testing 100% of cages in each affected or suspected rooms. Collateral testing *may* target animals belonging to investigators with positive cages in the quarantined room/suite/facility rather than testing 100% of the population. Depending on the extent and duration of the outbreak, sentinels in the facility may be periodically tested (more frequently than the quarterly schedule, usually monthly) as well.
- 6. The results of all tests will be forwarded by email to the SOM-ARC Chair and appropriate faculty and their staff on the same day that results are available.
- 7. The SOM-ARC Chair, in consultation with the ULAR Associate 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 (paragraph 3) testing show that there are still positive animals (evidence of a spreading infection), the room and/or suite may be depopulated and essential mice relocated to an off-campus 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

Policy No. RA-ANML-001

Page 5 of 15

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 Diagnostic Services 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 Assistant Dean for Animal Research and Executive Vice Dean 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 ٠
- 4. The Assistant Dean, in consultation with the Executive Vice Dean, will evaluate individual faculty requests and forward decisions to the faculty within 48 hours.
- 5. Until such time when on-campus housing exists that will not present health risks to other rodent populations, the SOM-ARC will identify an external vendor. Faculty must then obtain a vendor cost estimate (a formal quote), and submit this to the Assistant Vice Dean and the Executive Vice Dean for final approval. Faculty will work with the Office of the Executive Vice Dean to insure that appropriate Risk Management invoices are completed prior to shipment of any animals. The Office of the Executive Vice Dean will coordinate the request for reimbursement with Risk Management. 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 Diagnostic Services will notify investigators that the deadline has passed and ULAR staff will be authorized to 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.

V. CONTACTS

Executive Vice Dean and Chief Scientific Officer, 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

Policy No. RA-ANML-001 Page 6 of 15

Fax: 215.573.9438

VI. ATACHMENTS

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: MHV Policy Approved in 2005 **APPROVED:** 12/2/10 Executive Vice Dean and Chief Scientific Officer, SOM Date

Policy No. RA-ANML-001 Page 7 of 15

Attachment 1: MHV Reimbursement Process

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 Executive Vice Dean and Chief Scientific Officer via Nam Narain (<u>narain@mail.med.upenn.edu</u>)
- 4. Request should include the following:
 - a. Letter addressed to the Executive Vice Dean 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: <u>http://www.med.upenn.edu/genetics/core-facs/tcmf/</u>

Kathleen A. Thompson

Research Specialist

Tel: 215/573-3023; 215/746-6392

Email: <u>kthompso@mail.med.upenn.edu</u>

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 <u>http://www.criver.com/SRM/tgs/pdf/TG_FM_ModelInformationForm.pdf</u>
- 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

Policy No. RA-ANML-001 Page 8 of 15

- 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 <u>http://www.finance.upenn.edu/riskmgmt/propins.html</u>. 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.

Policy No. RA-ANML-001 Page 9 of 15

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

SERVICES AVAILABLE FROM THE TCMF CORE FOR PRESERVATION AND RE-DERIVATION OF MOUSE LINES UNDER CURRENT QUARINTINE 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, rederivation 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 use for IVF of wt eggs. The eggs will have to be harvested in the Core from vendor females (if

Policy No. RA-ANML-001

Page 10 of 15

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/genetics/tcmf/

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

Kathleen Mossbrugger Research Specialist Tel: 215/573-3023; 215/746-6392 Email: kthompsomaiLmed.upenn.edu

Policy No. RA-ANML-001 Page 11 of 15

Attachment 3: Request to Send Rodents to Other Institutions

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 two-page information sheet entitled *Request to Send Rodents to Other Institutions* to ULAR Diagnostic Services at least two weeks prior to the requested delivery date. Please note that the embossed original must be received in order to complete the request.

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; *identify cages containing these animals with a readily (colored) identifiable cage card labeled, "For shipment to (person) at (institution/destination)." The card must be dated and also must have the principal investigator's name, IACUC protocol number, and a contact name and phone number.* **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.

Do not sign or submit any agreement(s) — e.g. a Material Transfer Agreement — provided by the receiving institution without having it reviewed by the Center for Technology Transfer (CTT). Upon receipt of any such agreement or requests for signatures — or if you have questions of a legal nature — contact the CTT at 215-898-9591 (voice) or 215-898-9519 (fax).

ULAR coordinates all shipping arrangements through selected commercial carriers. Special arrangements using other commercial transport may be 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.

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 as to 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 Services at 215-746-0195 or via email to <u>ular-</u> <u>dx@pobox.upenn.edu</u>.

Policy No. RA-ANML-001 Page 12 of 15 Request to Send Rodents to Other Institutions

DATE:

Coordination of the shipping process typically requires two or more weeks; please plan accordingly. When completed, return this form to ULAR Diagnostic Services, 3800 Spruce Street, Suite 177E, MC 6009; or fax to 215-746-4146. NOTE: Embossed original must be received to process the request.

UNIVERSITY OF PENNSYLVANIA INVESTIGATOR INFORMATION

Principal Investigator:			Dept:
Campus Address:			
Phone:			
Contact Person (if different from P			
Phone:	Fax:	_ Email:	
IACUC Protocol #			
INSTITUTION TO WHICH ANIMA			
Principal Investigator:			Dept:
Phone:	Fax:	_ Email:	
Contact Person (if different from PI			
			ide contact info if not previously listed)
			. , ,
Addressee and exact address to be			
· · · · · · · · · · · · · · · · · · ·			
VETERINARIAN AT INSTITUTION	TO WHICH ANIMALS ARE BE	ING SENT	
Veterinarian:			·
Phone:	Fax:	Email:	
Animal Resources Contact Person: (if different from veterinarian)			
Phone:	Fax:	Email:	

Policy No. RA-ANML-001 Page 13 of 15

Request to Send Rodents to Other Institutions, page 2

INFORMATION REGARDING ANIMALS TO BE SHIPPED

Which of the following best describes the animal(s) to be shipped:

		background strain background strain		
Are animals immune competen			als: Male Female	
ADDITIONAL ANIMALS TO BE	SHIPPED (wildtype, negativ			
Strain/Genotype	Coat color	Gender	Quantity	
Animal location(s), include building				
UNIVERSITY OF PENNSYLVAN	IIA INVESTIGATOR			
INSTITUTION)"; include date, Pl managed facilities, place a blue a	als for the shipment with a c name, IACUC protocol #, an acetate overlay (available from	which necessitates a clinical examina age card labeled "FOR SHIPMENT ad contact name/phone number. For m husbandry managers) over the ca	TO (PERSON) AT (RECEIVING	
Check here to indicate that this h	as been completed:	Total # of cages marked:		
Provide any specific packing inst	ructions (e.g., separate by ge	ender, # mice/compartment, special i	equirements:	
•				
A patent application has been, or If yes, contact the Center for Tecl	will be, filed for any strain(s) nnology Transfer (CTT) at 21) for shipment: □ yes □ n 15-898-9591 to prepare a Material Tr	o ansfer Agreement.	
BILLING INFORMATION				
Cost will be incurred by (name of	individual):			
Billing number for administrative		bing costs incurred: 5234		
AUTHORIZATION SIGNATURE		JZJ4	[_]	
	· · · · · · ·			
Principal Investigator or Authorize				
Departmental Business Administr	ator:			
Business Administrator's Email A	dress:			
			· · · · · · · · · · · · · · · · · · ·	

Policy No. RA-ANML-001 Page 14 of 15

Business Administrator's Embossment: (required for processing)

Policy No. RA-ANML-001 Page 15 of 15

Attachment 4: Model Information Form—Transgenic Services

• Model information forms for transgenic services for the Charles River Diagnostic Laboratory may be found at <u>http://www.criver.com/SRM/tgs/pdf/TG_FM_ModelInformationForm.pdf</u>