



**General Operations
Standard Operating Procedures
V1.01, 11/1/2022**

1. Abbreviations and Terms

CC:	Coordinating Committee
CSR:	Customer Service Representative
DI:	Donating Investigator
EAC:	External Advisory Committee
Facility:	Any one of the MMRRC mouse repositories
ICSC:	Informatics, Coordination and Service Center
IT:	Informatics Technology Subcommittee
MMRRC:	Mutant Mouse Resource & Research Centers
Mouse line:	Mice and/or germplasm
OHM:	Operations, Health and Management Subcommittee
RI:	Requesting Investigator
SAC:	Strain Acquisition Coordinator (at ICSC)
SDS:	Strain Data Sheet, maintained by ICSC curator/administrator
SOP:	Standard Operating Procedure

2. Introduction

- a. This document describes the overall operations of the MMRRC Program:
 - A. Section 3: DI submission of applications
 - B. Section 4: ICSC processing of applications
 - C. Section 5: CC review and disposition of applications
 - D. Section 6: CC assignment of mouse lines to Facilities
 - E. Section 7: ICSC communication with DI
 - F. Section 8: Importation of mouse lines
 - G. Section 9: Management of mouse lines
 - H. Section 10: Distribution of mouse lines
 - I. Section 11: Billing for orders of mouse lines
 - J. Section 12: Statistical updates
 - K. Section 13: Miscellaneous issues
- b. The OHM is responsible for this document.

3. DI submission of applications

- a. DI shall propose donation of a mutant mouse line to the MMRRC CC by completing and

submitting an on-line submission application available on the MMRRC website at www.mmrrc.org

- b. There are three types of mouse line submissions (distinguished as either type 1, 2, or 3) based on information the DI provides on the submission form:
 - A. Type 1: Standard submission: Using established criteria (*see Appendix 1, Selection Criteria for Submitted Mouse Lines*), a DI submits their application to deposit their mouse line for review by the CC to determine whether the mouse line has sufficient value to be preserved using MMRRC funds.
 - B. Type 2: NIH pre-authorized submission: DI submits one or more mouse lines that have been pre-approved for transfer to the MMRRC repository, either by his/her NIH Program Officer or other NIH official. The depositor will be asked to identify the sponsoring institution or contract. Accepted lines are funded by the MMRRC.
 - C. Type 3: Contract submission: DI either has a contractual agreement with an MMRRC Facility or submits a mouse and/or ES cell line with funding to subsidize its preservation. In the latter case, the DI may indicate the MMRRC Facility into which to deposit the mouse line.
- c. A DI may choose whether to deposit their mouse line for unrestricted distribution, for distribution to not-for-profit entities only, or for distribution to non-profit under COU and for-profit under commercial license. There is an opportunity to indicate the choice on the Donor MTA form.
- d. The policies of the MMRRC and terms and conditions of mouse line acceptance are clearly stated in the application form and instructions; completion of the application shall indicate that the DI has read these policies, terms and conditions and agreed to them.
- e. In order to encourage submission of valuable mouse lines awaiting the first publication, a DI also may request that the mouse line not be released and distributed for up to 12 months after acceptance (*see Appendix 2, Delayed Release and Distribution Policy*). If granted, then the mouse line can be assigned and shipped to a Facility but will not be listed in the MMRRC catalog until it is published or the DI gives permission or after 12 months, whichever is sooner. Delayed release may be extended by vote of the CC.
- f. The DI shall electronically transmit the completed Stage 1 application form to the MMRRC-ICSC using the "submit" button at the bottom of the form.
- g. Accompanying the application form or submitted separately, the DI shall send any supplementary information, such as reprints or preprints of scientific articles, either by FAX, email attachment, and/or electronically to the MMRRC-ICSC.

4. **ICSC processing of applications**

- a. Upon receipt of an application, ICSC personnel shall:
 - A. receive, review, store, and compile all application materials.
 - B. assign a unique number to each mouse line submitted.
 - C. revise nomenclature to be compatible with current convention.
 - D. post the revised submission application form, and associated supplementary material, online at "Strains Ready for Review" on the MMRRC Strain Review website.
 - E. incomplete applications will be returned to the DI for completion.
- b. The ICSC Curator shall ensure the review materials for strains submitted up to the first

Tuesday of the month are posted on the internal website strain review page and the SAC shall assign strains for review to Facility and ICSC PI's no later than the second Tuesday of each month for review at the next monthly teleconference (third Tuesday of each month).

- c. Each application will be reviewed by a primary and a secondary reviewer from separate Facilities or ICSC, who will post their reviewer comments online. Reviews should be posted no later than the Monday prior to the CC teleconference to enable the SAC and others to see them.
- d. The SAC shall list in the monthly teleconference agenda any lines that are declined or that one of the reviewers' requests that the CC discuss.
- e. The SAC shall distribute the agenda to the CC one week in advance of the teleconference.

5. **CC review and disposition of applications**

- a. At the monthly teleconference, the members of the CC shall discuss and evaluate the merit of each Type 1 standard submission application that has been placed on the agenda by a reviewer (see 4D above), using the established criteria.
- b. One of 3 definitive decisions shall be made on each Submission Application:
 - A. Accept
 - B. Defer decision for additional information from DI, AP, or others
 - C. Decline

6. **Assignment of mouse lines to Facilities**

- a. Typically, assignment of mouse lines to a Facility takes place at the monthly CC teleconference.
- b. Before making assignments, the SAC shall review the history of recent Facility selections and a summary of current holdings of each Facility provided by the SAC.
- c. SAC shall assign each accepted Type 1 standard and Type 2 NIH pre-authorized submission mouse lines to a MMRRC Facility.
- d. SAC will send an email with the monthly strain assignments within 48 hours of the CC meeting.
- e. SAC shall acknowledge the submission and assignment of Type 3 contract submission mouse lines. If prior arrangements have not been made, the SAC shall also assign Type III submissions to a Facility with prior permission by that Facility.
- f. When possible, a mouse line will be assigned to the Facility geographically closest to the DI to minimize shipping expenses for the DI and minimize shipping/handling stress for the animals.
- g. CC members can request specific strains during the CC meeting if assigned to another Facility and work out the details of such assignment arrangements with the other Facility.

7. **ICSC communication with DI**

- a. The SAC or designee will participate in the monthly teleconference.
- b. Within one week of the same teleconference, SAC shall notify by email each DI regarding Provisional Acceptance, Defer, or Decline of their strain.

A. Accept: The SAC or Delegate shall indicate the strain is provisionally accepted,

and request that stage 2 of the submission be completed. Once completed, the SAC or Delegate will then provide formal acceptance to the DI, congratulating them, email copy the Facility, and request the Donor MTA and genotyping protocol.

- B. **Defer:** For deferred decisions, to collect more information from the DI, the SAC or Delegate shall contact electronically the DI and/or contact representative and indicate to the DI that failure to respond to a request for further information may result in rejection of their mouse line.
- C. **Reject:** The SAC or Delegate shall indicate *the reason for rejection* of the mouse line by the CC and inform the DI that they are welcome to submit a rebuttal to the CC via the ICSC. *The ICSC may suggest that the DI reapply to the MMRRC with additional information, apply as a Type 3 and sponsor the deposition, private sperm archiving if appropriate, or apply to alternative repositories (EMMA, JAX, MMHCC, etc) for submission.*
- D. **Rescind:** If stage 2 is not completed within a 6-month timeline, or the Donor MTA is not supplied within a 6-month timeline, the ICSC will discuss with the assigned center, and if, after multiple attempts to communicate with the DI by phone and email, there is no response, the line will be rescinded by email from the ICSC, the Facility will be copied. The Facility shall update the CC at the monthly CC meeting if the line is rescinded.

8. **Importation of mouse lines**

- a. The selected Facility to which the mouse line has been assigned shall contact the DI to arrange for receiving the mouse line and obtaining a genotyping protocol (if not already received by the ICSC), health certificate, and other supporting documentation.
- b. The DI or their institution must submit a completed and signed Donor MTA to the ICSC. The MTA is pre-signed by the ICSC institution official. The ICSC will update the records appropriately for the executed MTA and retain a copy on file.
- c. **Genotyping:** DI is expected to provide genotyping assay(s)/primers, tissue, or DNA etc. to Facility for PCR or another genotyping assay. DI may use a genotyping form provided by the MMRRC. The DI should have a reliable genetic testing screen for their mouse line and transmit a full and complete protocol to the Facility and the ICSC for publication on MMRRC web site.
- d. **Health Certificate:** DI shall provide a current health certificate from their institution. (Health Status does not affect the acceptance status of the mouse line; it is solely to assist the Facilities with managing the risk of contamination of their facilities.)
- e. Facility may recommend to the CC to discontinue acquisition of the mouse line (Rescind) should the DI fail to submit mice, requested assays, pedigree information, and/or any other requested data, etc., to the Facility within a six-month time period, unless there are unusual circumstances (e.g., PI move), following mouse line acceptance.
 - A. Facility will use all reasonable effort (e.g., email, telephone, fax, etc) to contact the DI or the DI's institution and/or representative to obtain animals and/or requested information to acquire the accepted mouse line.
 - B. Facility to which mouse line was assigned will notify CC at a regularly scheduled CC teleconference of any mouse line that has not yet been received after due diligence from Facility (e.g., greater than 6 months, no responses to emails and phone calls) from notifying the DI of acceptance of their mouse line(s) by the CC.

- C. If the DI is unable to provide mice and/or requested information, then the Facility shall inform the ICSC. The SAC or Delegate shall attempt additional contact via phone and email, and report back to the Facility.
 - D. If after due diligence, the Facility and ICSC staff still cannot contact the DI, or the DI's institution and/or representative is unable to assist in contacting the DI and/or provide the mice and/or requested information, then the Facility shall inform the ICSC, the ICSC will prepare a letter to terminate acquisition of a strain, addressed to the DI's institution and/or representative, and copied to the Facility. If no response then the Strain is rescinded, and the Facility updated.
 - E. The Facility shall update the CC at the monthly CC meeting if the strain is Rescinded.
- f. Material transfer and shipping to, and receipt by, Facility
- A. Accepted mouse lines may be submitted as one or more different materials, including live mice (prefer 2 – 4 male mice for sperm cryo only, or 4 males plus 10 females for embryo cryopreservation or rederivation if embryo cryopreservation or rederivation is required), or germplasm (minimally 5 aliquots of sperm or 80 embryos) including associated QC data (recovery rates, genetic QC). Under certain circumstances, such as the DI's colony is extinct, or too small to generate the desired number of mice, smaller numbers may be acceptable after discussion with the assigned Facility. Alternative formats such as preserved ovaries, and/or embryonic stem (ES) cells require discussion.
 - B. Irrespective of transfer method, DI assumes all shipping costs to transfer the accepted mouse line to the assigned Facility. If extenuating circumstances exist, the Facility may choose to negotiate alternatives with the DI.
 - C. Prior to giving DI approval to ship the mouse line, a Facility may elect to first receive DNA or tissue to confirm the genotyping assay and strain genetics, utilizing materials and instructions provided by DI.
 - D. Prior to receiving mice, the Facility may also request fresh fecal pellets for microbiome analysis.
 - E. Each Facility is responsible for developing its own shipping and receiving policies.
 - F. Receiving SOP includes health status, backcross information, genotype, genotype assay protocol, husbandry protocol if non- standard, founder # if transgenic, and other information which may be necessary to maintain the materials.
- g. After a strain has been accepted, ICSC shall indicate on the publicly accessible website and appropriate public List Servs that a new mouse line has been accepted by the MMRRC. Until the line is available for distribution, the strain will be listed as under development and users will be directed to the Register Interest form and given the opportunity to express interest in it. If delayed release of a strain has been approved by the CC, the strain is made public when the delayed release period terminates.

9. **Management of mouse lines**

- a. Upon receipt of mouse line materials:
 - A. Facility notifies ICSC upon receipt of materials of a mouse line, the

maintenance status, the preservation formats, and the available genotype(s) of a particular mouse line via the Importation Tracking application on the Internal Project Site. This information will be used to update the online catalog as appropriate. The Facility also indicates estimated availability date via the Importation Tracking database on the Internal Project Site. The Facility may need to revise date of availability multiple times based on progress of mouse line through receipt, genotyping verification, cryopreservation, and/or rederivation and development of a live breeding colony.

- B. ICSC shall track interest via the public MMRRC website; registered interest information shall be available anytime to the Facility; once available for distribution (e.g., from live colony or cryopreserved archive), the level of availability shall automatically be indicated in the catalog once the available date indicated by the Facility in Importation Tracking is reached. The ICSC will notify scientists who have expressed interest that they may now order the line via automated emails.
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- b. All mouse lines should be checked to ensure their identity. The Facility shall establish a genotyping protocol and verify the genotype of the mouse line to be cryopreserved. The Facility will supply to the ICSC a copy of their own protocol in suitable electronic form or standard hyperlink for publication on the public website and linkage from the SDS page.
 - c. The Facility shall establish a cryopreserved archive of the mouse line, following cryopreservation guidelines. Once established, processed material from each line will be divided for storage at two physically separate sites in alarm-monitored facilities.
 - d. Those mouse lines judged to have a high potential for distribution will be rederived and established after health status verification as live breeding colonies.
 - A. A Facility may maintain a newly received mouse line as a live breeding colony if it is predicted to have a high potential for distribution.
 - B. Mouse lines intended for maintenance as a live breeding colony should be rederived using a method (i.e., hysterectomy, embryo transfer) determined by the Facility, including oocyte donor strain to be used for cryo recovery and embryo archiving.
 - C. Each Facility will maintain quarantine/isolation, rederivation and expansion areas/colonies. Housing and animal care policies will be developed by individual Facilities. Facility will determine the minimum level of animals to maintain for each mouse line managed as a live breeding colony. Initial production expectations should be 1-2 breeder pairs per month.
 - D. Upon rederivation of mouse line into flexible-film isolator or other barrier facilities, an immediate health screen will be performed to verify the health status of the colony prior to distribution.
 - E. Distribution of a mouse line prior to full rederivation may be made by a Facility with prior full disclosure of health status to the requesting investigator.
 - F. The Facility shall apply the genotyping protocol provided, or establish a usable protocol, to verify the genotype of the mouse line, whether held as a live colony or as a cryopreserved.
 - G. All procedures, facilities, and animal care and use will be in accordance with an approved Institutional Animal Care and Use Protocol.
 - H. The Facility shall notify the DI that the mouse line will be retired to “Cryopreservation-only” maintenance and make a one-time offer to send at no cost (except shipping costs) live mice from the rederived colony to the original DI if requested prior to retiring the mouse line. If only cryopreserved material is

available, the Donor may receive a one- time, no fee (beyond shipping charges) delivery of an aliquot of cryopreserved sperm, as supplies allow. When giving material back to donor, the donor doesn't have to fill out a COU.

- I. A mouse line may be “retired” to “Cryopreservation-only” maintenance with sufficient justification, including, but not limited to, actual or perceived demand, breeding efficiency, and other considerations deemed appropriate by the Facility. The Facility may choose to enter a retire date prior to the actual date such that mouse lines to be “retired” to “Cryopreservation-only” maintenance are made public on the National website and emailed out to List Serves.
 - J. When possible, an RI expressing interest in live mice will be offered live mice at the live mouse cost from the rederived colony, such as that being used to establish the cryopreserved archive, before the live mouse line is retired.
 - K. Once a mouse line is fully retired to “Cryopreservation-only maintenance”, all RI, including the originating DI, will be required to pay resuscitation fees and, if requested, costs for specific genotyping if they wish to receive live mice.
- e. The CC and/or a Facility may recommend additional phenotyping and/or genotyping tests or procedures on any mouse line accepted by the MMRRRC Program and assigned at any Facility. The CC will decide by consensus the merit of the recommendation.
- A. If the recommendation is approved, the Facility at which the mouse line is assigned will be expected to ship a reasonable number of mice at the appropriate age, sex, and genotype at no cost to the Facility that will do the phenotyping.
 - B. If the recommendation is not approved, the Facility requesting the mouse line for analysis will be charged all appropriate shipping, per mouse, and/or other (i.e., cryopreservation) fees, as would any requesting investigator.
 - C. The ICSC and/or a Facility may define the level of backcrossing and/or congenic breeding after review of DI pedigree and discussion with the DI; the Facility may need to report only backcross generations at Facility if accurate DI information is not available. The ICSC considers a strain congenic after 5 backcrosses. Additionally, MUGA analysis may alter strain designation after review by the Facility and report to the ICSC.

10. Distribution of mouse lines (see also *Appendix 3, Distribution Policy*).

- a. Facilities shall be encouraged to make materials available for distribution as soon as possible after receipt of mice.
- b. All mouse and cell lines will be listed in the catalog and catalog entries will be linked to information about the associated line that shall be posted on specific electronic SDS files located online.
- c. All mouse and cell lines are distributable to not-for-profit entities, while some are distributable to for-profit commercial entities, as indicated in the catalog.
- d. The ICSC CSR shall look for missing or inconsistent (e.g., ship to does not match RI or bill to) information required to complete order prior to forwarding it to the Facility. This does not include billing-related information, which is currently handled by the individual Facilities.
- e. Ordering procedure (see *Appendix 4, Pricing Policy*):
 - A. All orders for mouse lines will be routed through the ICSC online Order Tracking System (OTS).

- B. Using the online Order Tracking System (OTS), ICSC CSR reviews the order and accepts it in the OTS, which then automatically forwards it to the Facility.
 - C. An RI's Institution Official (IO) or authorized representative must agree to the appropriate use agreement associated with the requested strain. RIs are provided an email upon ICSC order acceptance, explaining how to forward the email and link or document to their technology transfer office. CSR updates the order IP which is forwarded to the Facility once the MTA or COU is received. The Facility may have non-MMRRC agreements handled at, and updated by, the Facility.
 - D. Facility CSR accept the order by verifying the receipt of agreements, and checking appropriate field in the OTS, which activates an automated email to the RI confirming the order has been accepted by the Facility supplying the material(s). If the Facility, for some reason, cannot fill the request, Facility staff shall notify the ICSC CSR or contact the RI directly to explain, at the discretion of the Facility.
 - E. Facility staff contact and confirm order with RI, provide estimated costs and delivery date, confirm billing and shipping information entered in the order in OTS, and update the OTS as necessary.
 - F. Any RI changes to order made to the ICSC CSR shall be entered into the OTS order and communicated to the supplying Facility. Any changes requested directly of the supplying Facility shall be entered into the order in the OTS by the Facility staff. If the Facility must change an order, the RI shall be notified, and the change recorded in the OTS. In any of these cases, the reason for each change shall be documented in the OTS record.
- f. Each Facility develops its own shipping and distribution procedures.
- A. Facility will prepare all relevant documents and shipping form(s).
 - B. Facility will contact RI prior to shipment.
- g. Each Facility can request mouse lines from any other Facility. Facilities may also interact to share distribution efforts, such as center to center to RI for international shipments, or center to center for resuscitation, then to RI. The arrangements regarding these inter-Facility transfers will be determined by the Facilities involved in the transaction.
- h. Fast-track availability of mouse lines. Facilities shall be encouraged to make mouse lines available for distribution as soon as possible after receipt of mice. The minimum requirements for making a mouse line available for distribution shall be genotypic confirmation of the mouse line assigned to the Facility, and after beginning the rederivation and/or preservation (embryo and/or sperm) process. That is, mice of a mouse line assigned to and received by a Facility may be made available for distribution by the Facility as soon as the genotype is confirmed, and sperm have been harvested.

11. **Billing for orders of mouse lines**

- a. Each Facility shall gather necessary billing information (if not provided in the OTS request), bill RI and collect own charges.
- b. Fees are based on costs associated with an individual line, including such factors as the effort and number of supplies needed to archive, maintain, and recover a line, demand for the line, and per diem for maintenance, among other factors.

12. **Statistical updates**

- a. Facility staff shall update importation tracking as imported mouse lines are imported and cryopreserved.
- b. ISCS staff shall make monthly statistical reports readily available to the program and contracting program officers at DPCPSI. Additionally, annual reports are available upon request by NIH centers or donors.

13. **Miscellaneous issues**

- a. Assessment of Facility participation in the MMRRC Program
 - A. Each Facility is expected to share equally in fulfilling the roles and obligations of the MMRRC Program. This includes participation in monthly teleconferences, subcommittees, and other administrative activities.
 - B. Each Facility is expected to accept assignments of accepted mouse lines at the monthly teleconference.
- b. MMRRC Facility Technical Support
 - A. Facility will establish at a minimum phone number/service with voice mail or email address for information (such as husbandry, breeding efficiencies) on mouse lines at their Facility, and identify a Contact Person listed on the MMRRC Website.
 - B. RI may be referred to other online resources to answer questions.
- c. Addition of new Facilities
 - A. New Facilities joining the MMRRC National System will assume and share expectations and responsibilities already established by and for existing Facilities.
 - B. New Facility(s) will begin taking mouse lines at the next regularly scheduled CC teleconference after the Facility is awarded an MMRRC grant or, if ramp up time is required, at a specified time agreed upon by the new Facility and the DPCPSI program officer.
- d. Retiring Facilities
 - A. Collections, including mice, control DNA for genotyping assays, archived cryopreserved materials, and all records held by a retiring Facility will be distributed equitably among remaining existing Facilities within 3 months prior to the end of funding.
 - B. Until NIH funding-support terminates, a retiring Facility must minimize the disruption to the research community, continuing order fulfillment and order acceptance while lines are being re-established at the new Facility.
 - C. Whenever possible, orders placed prior to transfer should be fulfilled by the holding Facility.
 - D. A retiring Facility must minimize disruption to the MMRRC acquisition/importation process. Until funding ceases, a Facility will be expected to complete importation and cryopreservation of assigned mouse lines that have already been received or are in transit.

- E. Once transfer of a line is begun, requests for live animals from resuscitation may be delayed and reassigned to the new Facility by mutual agreement.
- F. Transfer of holdings should commence soon enough to enable replacement facilities to commence distribution and fulfillment of a retiring Facility's lines prior to the end of NIH-funding for the retiring Facility.
- G. Transfer of holdings to new facilities should be done in a manner that reliably preserves the archive, e.g., transfer in two partial shipments to minimize the risk of inadvertent loss due to external events during transit.