SECTION 6.0 – REPOSITORY PROCEDURES: APPLICATION, REVIEW, AND RELEASE

6.0. REPOSITORY APPLICATIONS AND REVIEW

6.1. REPOSITORY APPLICATION PROCESS

6.1.1. Independent Online Review of Available Resources

Applicants are encouraged to begin by independently reviewing online descriptions and summaries of available resources to determine whether to proceed with a formal request to obtain resources. Online descriptions and summaries include:

- SWAN Data summarized through Data Warehouse keywords and searches (swanrepository.com)
- SWAN Repository Samples summarized on Biospecimens Page (swanrepository.com)
    - Specimen types available
    - Summary of specimens by visit year
    - Volumes
    - Specimen collection info
    - By Race/Ethnicity

6.1.2. Step One: Inquiry Checklist Submission

6.1.2.1. Inquiry Checklist content and submission

The Inquiry Checklist is the first submission in the process of obtaining Repository resources and is found on the website (swanrepository.com). This brief initial assessment provides information describing the proposed study and the resources necessary to complete it, including which specimen types investigators may be interested in, volumes, and time points of interest, and inclusion/exclusion criteria of the proposed sample set and data set. *The Inquiry Checklist form can be found in the Section 6 Appendices.*

6.1.2.2. Define sample request and sample size

The Inquiry Checklist is submitted electronically to UM Repository staff, who use the information to confirm the availability of data and/or specimens and to provide investigators with sample size estimates. In many cases, sample requests are adjusted and refined based on information provided in this step. An estimate of total fees (section 7.2) for the sample set is provided to the applicant investigator.

6.1.2.3. Timing

This step can typically be completed with 10 business days.

6.1.3. Step Two: Full Repository Application Submission and Review

6.1.3.1. Repository Application content and submission

With adequate sample sizes, applicants proceed with the Full Application. This form is similar to NIH applications, including the major sections: Introduction, Specific

Aims and Hypotheses; Background & Significance; Preliminary Studies; and Methods & Materials. The full Application form is available to complete and submit online, via the Repository website (swanrepository.com). A preview of the Application (pdf document) can also be found there for applicants to preview questions and develop content before beginning their submissions. *The Repository Application form can be found in the Section 6 Appendices.*

6.1.3.2. SWAN Sponsor: Inclusion of a SWAN Investigator

There must be assurances that a SWAN investigator will join the approved investigation to facilitate the appropriate and effective utilization of the information resources provided to the grantee and to provide assistance to the investigators toward the successful completion of the project. This Repository project investigator is expected to have full status accorded a co-investigator on any research endeavor.

If the lead investigator of a Repository application is not a SWAN investigator, a SWAN investigator knowledgeable in the area of the proposed work must be included in the study. This person will be known as the SWAN Sponsor.

6.1.3.3. SRO Review

All submitted Applications are reviewed by the SRO (described in section 2.2). Completed applications are sent to three SRO members including a statistician for review. The SRO primary reviewers evaluate the project's specific goals and hypotheses, the research approach, sample size and power estimates and quality of the laboratory and analytical methods, ensuring that proposed scientific aims can be addressed with Repository resources, that the study has adequate power to address the stated aims, and that no overlap exists with SWAN core or ancillary protocols or with approved Repository protocols. Questions or concerns may be sent back to applicant investigators to respond to. Reviews and reviewer recommendations are sent to the full SRO for discussion and a vote. Possible outcomes are: Approve without revision; Approve with minor revision; Reconsider after more extensive revision; Reject current proposal.

6.1.3.4. SRAG Review

A SRAG review is conducted when any of the following conditions are true of applications:

- Genetic specimens are requested;
- Reserved specimens are requested; or
- No scientific peer review will be done on the proposal.

In these cases, the application and SRO recommendation are sent to the SRAG committee (section 2.3), and SRAG will review the quality of the science and evaluate the ethical use of the requested biologic materials. Their recommendation, along with that from the SRO, will be sent to SC for approval.

6.1.3.5. SC Approval

SWAN Steering Committee approval is required of all applications. There are 11 voting SC members, including the 7 clinic sites plus the Lab, the CC, the SC Chair, and NIA. This vote is conducted via confidential online polls or through the SWAN CC by email vote (from Vicky Palombizio), where votes are emailed from all voting members of the SC back to the CC (Vicky) and results forwarded to the Repository.

Site PIs abstain from voting on Repository applications that they or their SWAN co-investigators are contributing to.

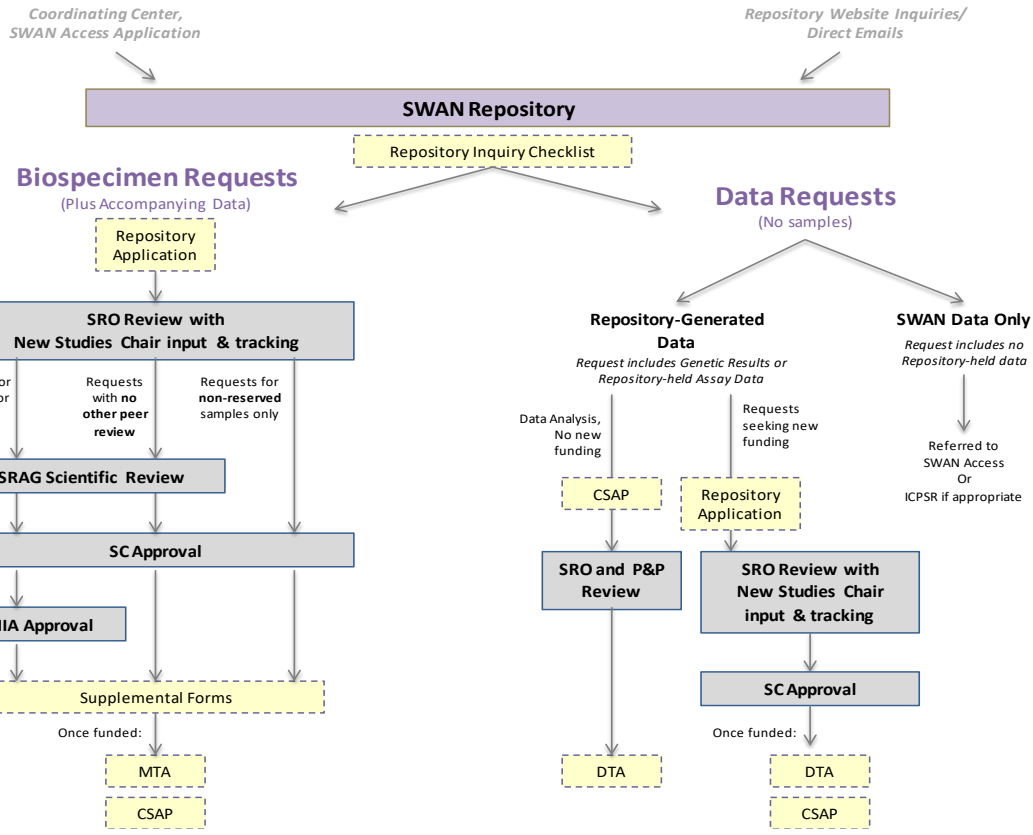
6.1.3.6. NIA Approval

A final approval from the Repository's NIA Representative is required for the release of any Reserved/Restricted or Genetic Samples. This is typically conducted by email from Repository PI to NIA Representative (Winnie Rossi).

6.1.3.7. Timing

Investigators are encouraged to have Repository Applications submitted, fully complete and with all questions answered, at least 6 weeks prior to a grant deadline. A letter will be provided to include with grant materials stating the approval to use Repository resources.

6.1.3.8. Schematic / Flow Chart of Repository Applications and Review



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6.1.4. Application Revisions

Applications not approved through Repository review may be revised and resubmitted. In the Introduction of the revised application, these proposals should include replies to any issues or concerns expressed in the initial review. There should be substantial changes in the content of the application, and these changes should be clearly marked for re-review.

6.1.5. Changes to Approved Applications Requiring Re-Review

Recognizing that resubmissions of grant applications frequently require modifications to scientific aims or study design, which may or may not change the scope or specimen requirements, this policy specifies the two situations when the SWAN Repository requires re-review and approval of such modifications:

1. Additional samples are requested.

2. There is a *substantial* change in aims or scientific scope of the proposal.

In these situations, an Amendment Letter to the SRO is required. The Amendment Letter should clearly point out the changes in the request and reasons for them.

If no reserved samples are requested, the SRO will review and approve proposed changes in specimen request.

If reserved samples are requested or if there is a substantive change in scope or aims of the study, the usual approval process will be followed.

6.2 POST-APPROVAL ACTIVITIES

For applications approved through Repository review, several additional actions take place before samples are released.

6.2.1. Award Letter

Notice of the Repository review approval comes officially in an Award letter from the Repository PI to the approved applicants. This letters states specifically which samples are approved and the associated estimated fees, and marks the date from which progress reports are due annually.

6.2.2. Supplemental Form for use of Genetic Materials

A set of agreements between the Repository and investigators approved to receive genetic materials is compiled in a Supplemental Form, which requires the investigator's signature to proceed with the sample embargo. On this form, investigators must discuss the likelihood that the proposed investigation would lead to the need for genetic counseling and are advised that they must be prepared to provide individual results in the event a participant requests them. *The Supplemental Form can be found in the Section 6 Appendices.*

6.2.3. Embargo

The approved set of samples is embargoed for the investigator(s) while project funding is secured. The embargo is granted for up to two NIH review cycles. Prompt updates are expected from Applicants on the outcomes of their grant applications.

If after two grant cycles, funding is not secured for the Repository-approved application, the embargo is lifted from the samples and they are made available to other applications.

6.2.4. Material Transfer Agreements (MTA) and Data Use Agreements (DUA)

MTAs are agreements required to transfer materials (any specimens) from the Repository to another institution. The SWAN Repository begins the MTA process once the approved application is funded. The MTA sets forth the terms for accepting Repository specimens. This Agreement and the application's Award Letter are sent to the receiving institution from UM's Office of Technology Transfer (OTT). The Investigator and his or her institution's officials sign the MTA and return to the UM OTT. Finally, the Repository PI signs for the Repository and the MTA is then fully executed.

In the case of applications only requesting Repository data (and no specimens), a Data Use Agreement (DUA) is used instead of a MTA. The DUA works the same way, but lays out terms for the appropriate use of data and how it should be disposed of after a certain period of time. *The Repository's MTA and DUA forms can be found in the Section 6 Appendices.*

6.2.5. Sample and Data Destruction Verification Forms

Both the MTA and DUA are accompanied by Destruction Verification Forms, which investigators use to document and verify that the Repository resources they received were disposed of in an appropriate way – limiting their use to the approved investigators for the specified aims. *The Repository's Destruction Verification forms can be found in the Section 6 Appendices.*

6.2.6. Concept Proposals for Manuscripts - to SWAN

Concept Proposal forms (CSAPs) for new SWAN publications are distributed to Investigators as Repository materials are released. These forms are submitted by the Investigator, along with the SWAN sponsor, to the SWAN P&P committee when the applications are funded. The Concept Proposal form is also used as an application for requests for data only (no specimens) not seeking new funding.

6.3. RELEASE OF REPOSITORY RESOURCES

6.3.1. Release of Repository Samples

Once the above steps are taken, including fully executing the MTA, the final approved sample pull list is submitted to Precision by the Repository Manager, along with contact information of the receiving laboratory and personnel. The lists are ordered by vial ID or barcode. If any vials are found to be missing or damaged, substitutes may be provided. A timeframe for pulling and shipping the specimens is agreed upon.

Standard procedures are strictly followed by Precision personnel retrieving the specimens to assure the highest sample quality throughout the pulling, QC, and packaging processes. Samples are packed into shippers on dry ice, in accordance with federal and IATA shipping guidelines. Prior to shipment, email notifications are sent from Precision personnel to the contact person at the receiving lab and to the Repository manager with notice of the outgoing shipment and FedEx tracking numbers, and confirmation that the lab is able to receive the shipment.

The samples are shipped via FedEx overnight service. Precision follows up with the lab, confirming the receipt of shipments in good condition.

6.3.1.1. Relabeling Requirements for Release of Samples from 2 Sites

Following requirements set forth by the IRBs of 2 SWAN sites in 2014 (see Section 3.1.2.1 for details), all vials from non-consenting UC Davis participants and all Core vials from Chicago must be relabeled prior to release from the Repository. This involves removing the current label and replacing it with a new label displaying only the original barcode. Precision has developed appropriate procedures to include this extra step in processing outgoing SWAN batches. (This requirement does not affect DNA samples.)

6.3.2. ID Encryption of Released Samples

At the same time the samples are being shipped, the Repository manager sends an electronic manifest to the Investigator and receiving personnel at the laboratory. This manifest lists the samples in the shipment - by Barcode (Tube ID, matching the vial label's barcode) and Encrypted study ID (EID). The EID replaces the regular 7-digit SWAN ID, and is consistent for participants across all visit years. The EID is unique to each application, with the application number appended to the newly auto-generated alpha numeric code constituting the EID.

6.3.3. Release of Repository-coded data sets

SWAN phenotypic datasets without personal identifiers are built, including variables as specified by the end-user and encrypted IDs (EIDs) matching the electronic manifests. SWAN ID encryption adds another layer to assure confidentiality. Detailed codebooks are built for each data set including a data dictionary, methodological description and descriptive statistics.

6.4. DIFFERENT TYPES OF APPLICATIONS

The process above describes the steps taken for the application and review of new Repository applications requesting biospecimens. Below are the modifications in the process for different types of Repository applications.

6.4.1. New Applications, for Data Only

If a new Inquiry Checklist submission indicates interest in SWAN Core data only (no Repository specimens or data), Investigators are referred to the SWAN CC (SWAN Access) or to the publicly available Inter-university Consortium for Political and Social Research (ICPSR) data sets if appropriate.

If a new Inquiry Checklist submission indicates interest in Repository data (but no specimens), then these steps are followed:

6.4.1.1. Data-only Requests for Repository Data, Seeking New Funding

In these cases, applicants submit the full Repository Application to SRO, as usual, and must get SC approval. (SRAG and NIA approval is NOT required.) Once funded, these applications sign a DUA instead of an MTA.

6.4.1.2. Data-only Requests for Repository Data, Not Seeking New Funding

In this scenario, applicants need only to complete the CSAP (in place of the Repository application) and submit it to the SRO and P&P simultaneously, which is the only review necessary for approval. Once approved, a DUA is signed between the Repository and institution receiving Repository data.

6.4.2. Supplemental Applications

If an Investigator is interested in requesting additional data and/or specimens to expand the scope of a previously approved and completed project, *and is staying within the originally approved scientific aims*, a supplemental application can be submitted. A supplemental application includes a progress report and evidence that expanded access will substantially enhance the impact of the research findings. The original aims and sufficient information from the original application should also be submitted to allow evaluation of the proposed supplement in relation to the goals of the original proposal. Supplemental applications are reviewed by the same committees as a new application would warrant, depending upon what materials are being requested.

6.4.2.1. Extensions of the 2006 Genetics Supplement Papers

In the case of an investigator requesting to extend the protocols from the Papers of the 2006 Genetics Supplement of the Am J of Med (Repository Protocols P01-P19), the following application process should be followed: (2012 precedent, J Bromberger, extension of baseline study of depression (P16) to all of SWAN.)

Investigator should submit CSAP to Core SWAN and the Repository, which is reviewed by SWAN and SRO genetics members. The data will remain encrypted, with EIDs in place of SWAN IDs.

Note: a new or amended MTA is necessary if a) additional genetics data is requested (additional SNPs) or if b) the data will be received by an institution other than the original institution.

6.4.3. Hybrid Applications

In the situation where an application includes both a Repository request and a *new data collection* component, applications are submitted through the Repository, but must meet application requirements of both the SWAN Repository and New Studies. These applications will be reviewed by the SRO with an expanded application and review process to comply with New Studies Guidelines.

Most applications to the Repository require dialogue between the Repository and the PI submitting the hybrid application, by which the Repository requests clarification and additional information. The deadline for the submission of the initial draft of the proposal is 10 weeks before the grant proposal is due to the funding agency. The review of Hybrid Studies is anticipated to take 4-6 weeks, once a complete proposal is provided, having all questions from the Repository answered and resolved.

1. *Identification of the appropriate review process* will be addressed by including a question in the Repository Inquiry Checklist asking whether the Repository application also involves the collection of new data from SWAN participants.

2. *Additions to the Repository Application* if the application includes new data collection will include sections on:

    a. **Subject eligibility/recruitment**: Provide a detailed explanation of the study participants to be included in your proposal. Include which site(s) will be used in the proposal.
    b. **Data management issues**: If applicable, provide details on how the data will be collected, entered, processed and/or cleaned. Include information on quality control measures that will be implemented in your study.
    c. **Integration with and impact on core**: Explain how your proposal will be merged into the main SWAN study. State whether any SWAN Investigator can sign up for authorship during the publication phase or whether publication sign-up will be limited to ancillary studies.
    d. **SWAN participant burden**: Indicate whether participant time will be needed to accomplish your aims. If participant time will be involved, estimate the amount of time needed by each participant.

3. *The review process* for hybrid applications:
   a. The chair of New Studies will be appointed to be one of the SRO primary reviewers and review the application with respect to both Repository and New Studies requirements and guidelines.

   b. The New Studies chair will designate one additional reviewer from the New Studies Committee who will review the application with respect to the New Studies requirements and guidelines.

   c. A senior member of the CC will be asked to serve as the statistical reviewer for the Repository statistical review and will also review to assess the feasibility of the data collection and data management plan for the New Studies/new data collection component of the application.