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7.0. SWAN REPOSITORY PRACTICES AND POLICIES

7.1. SAMPLE USE POLICIES

7.1.1. Furthering the SWAN Mission

A major factor influencing the decision to release SWAN Repository samples is whether the aims of the application align with the SWAN mission to help scientists, health care providers and women learn how mid-life experiences affect health and quality of life during aging.

7.1.2. Use of Validated Assays

Applications for Repository specimens should include evidence that the proposed assay has been fully validated. Repository specimens are not released to applications aiming to validate new assays, unless approved by the SRO. Tests for assay validation, such as “Test for Ligand Specificity” and “Test for Comparability of Results” are described in the “Assay Validation Criteria” found in the Section 7 Appendices and distributed to applicants when appropriate.

7.1.3. Reserved Samples

7.1.3.1. SWAN Definition of Reserved Samples

To help protect the overuse of the Repository’s most valuable samples, defined by both scientific importance and scarcity, the Repository has identified and flagged

certain specimens as "Reserved". The SRO and SWAN SC approved the following definitions for Reserved samples in the SWAN Repository:

a.) **Serum**: All of the baseline serum collection is considered reserved, due to both scarcity and increased scientific value. For all subsequent visit years, serum vials can be identified as Reserved based on the combination of two factors:

- "Clean Post" indicating whether or not this participant would go on to have a natural menopause transition (defined as "not reporting any Hormone Therapy use before or at the first visit she was classified as post-menopausal").
- "Scarcity" or Vial Count per Visit Year.

ORIGINAL, 2012

In SWAN studies participants with a clean menopausal transition have a higher scientific value, therefore vial counts of 10 or fewer per visit year are flagged as Reserved. Serum from women without a clean transition are Reserved when 5 or fewer vials remain. The last serum vial for any woman at a visit year is flagged as restricted.

The following table shows the cut-off points for reserving Repository serum samples based on these two values:

IF CLEAN POST=	And SCARCITY =	THEN 'RESERVE' FIELD =
Clean Post = No	2-5 vials left	Reserved
Clean Post = Yes	2-10 vials left	Reserved
(either)	1 vial left	Restricted

REVISED, 2015

In the Fall of 2015, the SWAN Repository examined the consistent voting patterns from reviewing committees. These patterns suggested it would be worthwhile to consider lowering the bar for Reserved serum to reduce time of application review, reduce committee effort and increase utilization.

Therefore, the recommendation was made and approved to move the Reserved cut-off line for the clean-post women down from 10 or fewer serum vials available to 5 or fewer for all women. With approval from SRO, SC and NIA, the current definition of Reserved Serum is:

IF SCARCITY =	THEN 'RESERVE' FIELD =
2-5 vials left	Reserved
1 vial left	Restricted

Note: Review would still give special consideration to requests for baseline and clean post samples.

b.) **Plasma**:

1. **EDTA Plasma** is all reserved due to scarcity. Across study visit years, only 1-3 vials of EDTA plasma remain.
2. **Citrated Plasma** is not reserved, as this resource has not been utilized.

c.) **Urine**: Urine samples are plentiful in the Repository and are therefore not considered Reserved.

d.) **DNA**: SWAN Repository DNA is renewable through expansion of the EBV-transformed cell line and extracting new DNA. It is therefore not considered Reserved.

7.1.3.2. Specific Guidelines for Use of Reserved Samples

The following guidelines were established to support decisions by the SRO and SRAG to release Reserved and Restricted samples:

- Reserved samples should not be used if the question can be answered using other available samples.
    - Other available samples include non-reserved SWAN samples from other comparable women, from different time points, and/or non-pristine samples.
- Reserved samples should not be used for exploratory investigations or very preliminary hypothesis testing.
    - Prior scientific evidence should exist to justify the hypothesis/proposed analyses.
- Reserved samples should be used to substantively advance scientific knowledge and for innovative science.
- The use of Reserved samples should be more strongly considered for studies that are consistent with the mission of SWAN.

7.2. THE COST RECOVERY PROGRAM

7.2.1. Initialization of the Repository's Cost Recovery Program

The SWAN Repository responded to the directive of NIA to establish a cost-recovery mechanism to help support the expenses involved in the biobanking of SWAN specimens. The fee schedule was developed based on actual collection, processing, storage and distribution costs, and is reviewed and approved by the University of Michigan's Office of Financial Analysis on an annual basis. Official quotes are provided to individual applicants when the final sample selection is defined. Fees are the same for both SWAN Investigators and non-SWAN Investigators.

7.2.2. Current Fee Schedule

SWAN Biospecimen Costs – per vial

	Serum, Plasma, Urine	Extracted DNA	Transformed Cell lines
Direct Costs	$18	$65	$148
Indirect Costs*	+30%	+30%	+30%

Rates are valid through 10/21/2015.

SWAN Application & Data set fees

	Application Processing Fee	Encrypted Data Set Construction Fee
Direct Costs	$400	$950
Indirect Costs*	+30%	+30%

Rates are valid through 10/21/2015.

*Indirect costs apply to non-University of Michigan applicants.

7.2.3. Exemption / Reduction of Repository Fees

All exemption/reduction requests require NIA approval. There have been instances when an exemption from or a reduction in recharge fees was granted to Repository applicants. Precedents include:

In 2013, Application #052 NELA (Lasley) requested a waiver of the Repository's recharge fee for his small intramural project using DHS urine specimens. Special consideration was given to this case because 1) the requested samples were urine (particularly, DHS urine) which is plentiful and being considered for reduction, and 2) it was for a pilot study being used to test an idea where limited, and often only internal, funds are available. NIA approved the exemption.

In late 2013 – early 2014, Application #054 Melatonin (Greendale) requested a reduction in Repository recharge fees to a feasible amount, in her request for over 50,000 DHS urine samples to measure melatonin in over 2,500 cycle in the DHS study. The recharge rates per vial, for that many samples, made the cost prohibitive (more than $1 million). Completely waiving the fee was not an option as the Repository did not have funding to cover the cost of pulling and shipping such a large volume of sample. Permission was requested from NIA to reduce total costs of the recharge (including UM required indirect on the recharge amount) to $220,000- the maximum amount Greendale was allowed to include in her grant budget. Special consideration was again given because the samples requested were urine (particularly, DHS urine), and the release of this large of volume of samples had the potential to reduce overall storage costs. NIA approved the reduction.

7.3. RETURN OF DATA TO THE REPOSITORY

New data created from the analysis of SWAN Repository specimens must be returned to the Repository within 3 years of end of grant funding, as specified in the MTA. It is the responsibility of the Study PI to return results in a timely manner. Once returned, these data become a part of the Repository's Data Warehouse and are available to the Scientific Community through future Repository applications.

7.3.1. Standard Data Return

Typically, approved and released Repository sample manifests are encrypted to match a limited set of SWAN data which specifically supports the study's approved aims. The encrypted IDS (EIDs) make the datasets unique and no longer linkable to the rest of SWAN data. (If additional variables are required during the course of analysis, they must also be encrypted to match.)

In these cases, the Standard Data Return process applies for returning newly generated data to the Repository. Investigators work with protected (genetic and non-genetic) assay results for a period of up to 3 years-post funding.

- Advantage: Additional protected time to publish from generated results.
- Disadvantage: Samples and SWAN data are encrypted (to match). Additional variables needed must also be encrypted.

7.3.2. Integration with SWAN Core

Non-genetic assay results returned to the Repository are eligible for integration with SWAN Core data. These data are then managed at SWAN's Coordinating Center (CC). EIDs are un-encrypted and these data contain the common SWAN ID. Approval for integration is granted after review and consultation with the Study PI and SRO. In general, only data that are obtained on all or a substantial proportion of SWAN participants is considered eligible for integration.

7.3.3. Expedited Data Return Option

SWAN investigators working with non-genetic Repository materials (serum, plasma, or urine) have an expedited data return option. They may opt out of the ID-encryption, allowing the sample results to be linkable to all SWAN data. However, in choosing this option, they must also agree to return the assay results immediately to the Repository and SWAN Coordinating Center, and thus the scientific community, without a protected window of time.

- Advantage: Repository samples and SWAN data sets do not get encrypted; SWAN data retains regular 7-digit SWAN IDs.
- Disadvantage: Generated results are open for use by other approved SWAN investigators and scientific community.

This option is available for any SWAN Investigator using non-genetic Repository materials, and is working under the auspices of the SWAN Laboratory (CLASS). The SWAN V work is one scenario where the expedited data return option was employed.

7.3.4. Steps to Return Data

1. Instructions to the requestor about materials to be returned should include:
    a. *A final dataset*, with EID and newly-generated values & variables (SAS or Excel format). This should include the name of the analyte(s), units of measure, EID and visit. If values are analyzed in duplicate or triplicate, individual values should be provided rather than a summary value.
    b. *A codebook*, with descriptions of all new variables along with relevant response codes, when applicable (Word or pdf format). This codebook should include documentation about all included variables and their coding.
    c. A 1-2 page *Assay Description and Protocol* (Word or pdf format)
    Identify if this is a proprietary protocol, and what kits or major reagents were used (identify with manufacturer's name and lot numbers of kits for future comparability, plus QA information about how well the assay has been performing). Include

boundaries of lower limits and upper limits of detection (if relevant). Also include the laboratory where the analyte was run, as well as the address and lab manager or director's contact information.

2. When these documents are assembled and complete, please contact the Repository for a secure transfer site (do not email data). A transfer site will be established and a link to the site will be emailed to you.
3. Data descriptions are then added to Repository Data Warehouse catalog. Data will be available to subsequent Repository applicants.
4. If a request to integrate with SWAN Core data is received:
    a. Review and consultation will be sought from the Study PI, and then from the SRO.
    b. Final dataset will be prepared for SWAN CC, decrypting EIDs back to normal 7-digit SWAN IDs.
    c. Data and documentation will be securely sent to CC.

NOTE: Data can be returned at any time prior to 3 years after grant funding ends (or as specified in the MTA). Investigators may continue to work on the papers relevant to the approved original aims of their study as long as CSAPs are submitted and approved.

7.4. MARKETING AND ADVERTISING CAMPAIGNS

An advertising campaign was launched in 2013 and again in 2014, to promote the utilization of specific types of specimens unique to the SWAN Repository. SWAN Repository resources were advertised in relevant scientific journals and at relevant scientific meetings.

Journals in which Repository ads were ran include: *Menopause, Fertility/Sterility, Climacteric, JCEM Endocrine News, J Gerontology, Epidemiology,* and *Am J Epidemiology*.

Annual scientific meetings at which Repository ads were included in program materials include: International Menopause Society (IMS), North American Menopause Society (NAMS), International Congress of Endrocrinology (ICE/Endo), and the American Society for Bone & Mineral Research (ASBMR).

These advertising campaigns were considered successful. After each publication or meeting, we saw an uptick in the number of hits to the data warehouse. Our web audience increased from an average of less than 50 new users per month to over 100 new users per month in 2013 and 2014 during advertising periods. We had planned to expand the scope of this advertising program to include scientific journals focused on genomics, metabolomics, and proteomics, and promoting utilization of SWAN resources to specific scientific groups and Institutes who have relevant research programs, however no funding for these activities was available in the no cost extension year.

7.5. PRECISION BIOSERVICES PROCEDURES (confidential – restricted access)

These procedures describe the processes for handling SWAN specimens at the Precision Bioservices facility. Because they are proprietary and confidential, requiring the expressed

approval from Precision Bioservices to copy or release them, they are only listed here by number and title, and are kept in locked file by the SWAN Repository manger.

Precision Bioservices is accredited by the College of American Pathologists (CAP) Biorepository Accreditation Program (BAP) and is ISO9001 and ISO 13485 certified. Precision performs tasks under Standard Operating Procedures, and follows ISBER and NCI Best Practices for Biorepositories and applicable IATA shipping procedures.

7.5.1. List of Precision Standard Operating Procedures (SOPs) on file:

SOP25330 (SWAN Study Specific Information) SWAN Core Procedures

SOP25220 (Receipt of Incoming Frozen Samples) Incoming shipments handling

SOP25205 (Inventory of Incoming Frozen Specimens) Sample inventory

SOP25104 (Forms data entry SOP)

SOP25204 (Outgoing requests)

SOP25347 (Aliquot Procedures)

SOP25308 (Inventory Investigations Protocols)

SOP25204 (Lab Processing, Outgoing Shipments)

SOP712.01 (Business Continuity, Disaster Response and Recovery Plan)