3.0. SWAN STUDIES [GIVING RISE TO REPOSITORY SPECIMENS] AND INFORMED CONSENT

3.1. SWAN CORE STUDY

3.1.1. Brief Study Background

SWAN's core study was designed as a prospective, multicenter, multiethnic, multidisciplinary study of the natural history of the menopausal transition in women. An initial cross-sectional survey was administered to 16,065 women aged 40-55 women across the seven clinical facilities. From that group, eligible women were identified to continue in the longitudinal study, resulting in a longitudinal cohort of 3302 women. Clinic visits included questionnaire administration, physical functioning measurements, and additional protocols which varied between sites. An early morning blood draw and urine collection were also part of each visit. A portion of these specimens were collected for the purpose of being stored by the SWAN Repository for future use.

3.1.2. Consent for Core Specimens in the Repository

All women participating in the SWAN Core study went through an informed consent process. Participants were given options to participate in the Core studies (which include the procedures done at all 7 SWAN clinic sites); Sub-core studies (done at more than 1 but less than 7 clinic sites, such as the Bone study); and Site-Specific studies (done at one particular site).

The procedures in SWAN are classified as "minimal risk". All participants signed a detailed consent document explaining the purpose, risks and benefits of the proposed research, which is approved by the local SWAN site IRB for each study visit. Each site also was directed to include

specific language regarding the contribution of blood and urine specimens to the Repository for future use.

3.1.2.1. Core IRB/PHI issue for Repository specimens (2014)

In 2014, a series of special meetings were held to review whether information recorded on the vial labels of specimens stored in the Repository was considered PHI (protected health information) and whether further actions were necessary to comply with IRB regulations at any of the 7 SWAN clinic sites. Specifically, in addition to a unique sample barcode, the vial labels included participant initials and date of collection, which had been part of the specimen collection protocol to help resolve potential discrepancies if tubes were found without accompanying paperwork and vice versa.

Each site raised the issue with their local IRB after review of their consent documents. IRBs at five sites classified the stored specimens as research samples based on the current operational structure of the SWAN Repository. IRBs at two sites, UC Davis and Chicago, determined that because of affiliations with health systems, the initials on the vials constituted PHI and required removal prior to redistribution.

UC Davis participants were recontacted, and 283 women (as of 2/24/2016) gave special consent to store and distribute their samples as labeled. In total for UC Davis, samples at the Repository from 293 women (including the 283 reconsented women, plus 10 deactivated) will not require relabeling, however samples from the remaining 168 UCDavis women will be relabeled at the time of distribution. For Chicago, only the Core samples are affected, as consent forms for the DHS stored samples had specific language addressing their storage for future use. Protocols were established to ensure this relabeling requirement is met for the non-consenting UC Davis samples and for all Chicago Core samples before leaving the Repository.

DNA samples were not affected as the vials and labels were not created at the sites, and do not contain initials or dates.

3.2. DAILY HORMONE STUDY (DHS)

3.2.1. Brief Study Background

The Daily Hormone Study (DHS) is a sub-study of SWAN, developed to provide a more complete understanding of the variation in hormone concentrations throughout menstrual cycles of the peri-menopausal transition and to characterize changes of within-cycle events. A subset of 900 SWAN participants, coming from all sites and ethnic groups, participated in the DHS sub study by completing daily diaries about symptoms and feelings, and collecting urine samples every morning for one complete menstrual cycle or for up to 50 days, each year until the participants became post-menopausal. Samples from these daily urine collections, along with a serum specimen, are available through the Repository.

3.2.2. Consent for DHS Samples in the Repository

A separate form was used to obtain informed consent from the DHS participants. Each of the seven SWAN sites consented participants with their own IRB-approved forms. Specific language was included about Repository storage and future use. (See also 3.1.2.1, UC Davis samples require relabeling prior to redistribution.)

3.3. SWAN DNA STUDY

3.3.1. Brief Study Background

As one of the Repository's original aims, a SWAN DNA Collection was established. A one-time draw of whole blood was obtained from a subset of the SWAN participants. In addition, a mouthwash sample was collected to obtain buccal cells. This special collection took place in 2002-2003, spanning Follow-up visits 04-06.

DNA was extracted from blood cells of the whole blood sample, and used by the Repository to genotype several genes in the sex steroid hormone pathway. These genotype results are stored and available via the Repository application process, along with the DNA and immortalized cell lines which were created through EBV (Epstein-Barr virus) transformation. (For details on DNA processing see section 4.3.)

Although SWAN DNA samples were collected by all 7 Study sites, the SWAN New Jersey site subsequently requested that all genetic specimens obtained from their participants be destroyed (2006).

3.3.2. Consent for DNA samples in the Repository

All SWAN participants were given the option to participate in the DNA Study. The final collection includes 1538 women who consented to DNA and contributed a sample which successfully went through EBV (Epstein Barr Virus) transformation. Each site consented their participants using their own IRB-approved forms. Consent forms included general methodology of obtaining and processing the specimens, as well as the right of the participant to request information that becomes available as a result of any research. Participants were given the option to agree to each item below individually:

- To provide a whole blood sample;
- To provide a buccal cell sample;
- To have cell lines created from their samples.

The participants completed 3 copies of the consent form. One copy stayed at the site, one copy remains with the participant and a third copy was sent to the Repository. To ensure participant confidentiality, the copy that was sent to the Repository did not include the participant's signature or initials, but instead had a label that linked the consent form with the specimens which were provided by the participant. (The Repository copy of the informed consent was later destroyed at McKesson at the time the collection moved to SeraCare Bioservices.) The consent form was included with the specimens when shipped to the Repository. Specimens were

not processed if they were received without the Informed Consent Form. There was a seven-day reconciliation period in which any discrepancies could be resolved before the sample was destroyed. *Copies of the DNA Consent Forms can be found in the Section 3 Appendices.*

3.3.2.1. Returning Genetic Results to SWAN Participants

The DNA Informed Consent explicitly states that SWAN is not allowed to contact the participants to convey genetic results discovered through any Repository studies. However, participants can initiate contact with SWAN if they choose to learn if results have been obtained from their samples. Therefore, investigators using SWAN DNA and genetic samples are obligated to be prepared to provide individual results if a SWAN participant contacts her SWAN clinic site or the Repository inquiring about DNA test results. Investigators also need to be prepared to provide Genetic Counseling to affected SWAN participants if appropriate.

3.3.3. Certificate of Confidentiality adds Privacy Protection

The SWAN Repository obtained a Certificate of Confidentiality (MH-AG-01-02) from the Department of Health and Human Services, which, as provided in section 301(d) of the Public Health Service Act 42 U.S.C. 241(d), states:

> *"Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."*

The Certificate of Confidentiality mitigates the risk of involuntary release of genetic information for both the Principal Investigators and the participants. The protection afforded by the Certificate is permanent with respect to subjects who participate in the research during the time the Certificate is in effect (1/9/2002 through 5/21/2005). All DNA samples were collected within this timeframe. *A copy of the Repository's Certificate of Confidentiality can be found in the Appendix, Section 3.*

3.3.4. Review of IRB Restrictions for DNA

In January 2012 a group consisting of S Sherman, S Harlow, Dan McConnell, G Greendale, C Crandall, S Kardia, D Evans, and S Merillat met to review the sites IRB documentation for DNA collection; to discuss the consequent limitations and required procedures for DNA-related research; to discuss potential Bone and GWAS proposals and enhanced genome-wide exome resequencing; and strategies and priorities for generating additional genetic proposals.

The committee set forth the following guidelines after reviewing Repository IRB and informed consents from all six sites contributing DNA:

"It is our considered opinion that the IRB and consent documents require that:

1) The SWAN REPOSITORY and SWAN must have a high level of involvement in oversight of stored DNA samples, including review of the science by the SRO and the appropriate scientific advisory committee.

2) All data generated from Repository samples, including DNA data, must be returned to the SWAN Repository and incorporated into the databank accessible to SWAN researchers. Current policy, per agreements which all Repository material grantees must sign, is that investigators will return their result data sets to the Repository within 3 years of the end of the grant funding period.

3) DNA-related data generated from DNA samples must be anonymized. Thus,
    a. SWAN data provided to investigators conducting DNA studies contain new encrypted IDs, known only to specified staff of the Repository, as the Trusted Broker.
    b. DNA results requested for subsequent analyses by SWAN investigators also require encryption. Requests for this data must be made to the SWAN Repository via an Application, and individual datasets for these analyses will be generated by the Repository.
    c. At the time that SWAN and the SWAN Repository is terminated, all DNA material and identifying information linking DNA results to the SWAN data must be destroyed.
    d. SWAN can place genetic results in dbGaP (the Database of Genotypes & Phenotypes, from the National Center for Genomes & Phenotypes), as these data are anonymized and the process for utilization of the data requires application, scientific review, IRB approval, a defined timeline for utilization and annual reports. When required as a condition of funding, only the specific genetic results and a limited amount of phenotypic information are required to be posted. Anonymization of the data is the standard in the field."