

NASA Biological Specimen Repository Requirements

**Use and Storage of Specimens and/or Data from Human
Subjects for Current or Future Research**

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1. Introduction

A biological specimen repository is a secure controlled storage facility that is used to maintain biological specimens over extended periods of time, under well-controlled conditions, for future use in approved research protocols. The NASA Biological Specimen Repository (NBSR) has been established to collect, process, annotate, store, and distribute specimens and associated clinical data in a standardized manner in one physical location. All databases and repositories must comply with the requirements of the Federal Policy for the Protection of Human Subjects (Common Rule codified at 14 CFR Part 1230 and 45 CFR Part 46, NASA NPD 7100.8D and NPR 7100.8A) and the requirements of the HIPAA Privacy Rule.

The Committee for the Protection of Human Subjects (CPHS) is the federally mandated Institutional Review Board (IRB) at NASA. CPHS approval is required for all proposed research that is defined by 14 CFR Part 1230 and 45CFR Part 46.102(f) and NASA NPD 7100.8D and NPR 7100.8A. CPHS is also responsible for oversight and review of all repositories or specimen databases that could be used for future research purposes. By reviewing and approving protocols and specifying the conditions under which data and specimens may be accepted and shared, CPHS ensures ethical protection of the research subjects and protection of subject privacy and data confidentiality. CPHS has the authority to convene an advisory board to oversee privacy and confidentiality procedures and to provide another layer of review. A member of the group whose biological specimens will be stored serves as a member of the CPHS.

2. Research Protocols

Research protocols that include collection and storage of human specimens fall into two main categories, both of which require CPHS review and approval of specimen use. Prospective studies must obtain approval for collection and storage of specimens for defined current or future research needs. Retrospective studies must obtain approval for the use of samples that were previously collected and, in some cases, stored.

For prospective studies, the following guidelines apply:

- A. Specimens and data collected for undefined future research that could be shared, re-used, or stored for research purposes beyond the original scope of the approved CPHS application, should be banked in a research repository.
- B. Existing specimens and data collections that may receive specimens from future investigations should be banked in a research repository. The use of pre-existing specimens for research requires CPHS approval.
- C. Specimens may be stored for future research use. If the future use cannot be specified, or is significantly different from the original plan, then future CPHS approval is required before using the specimens. The principal investigator (PI) will be required to obtain written permission from each subject before using that subject's specimen in this or any subsequent study.
- D. Prospectively collected specimens obtained for clinical or diagnostic purposes may be used for future research purposes if prior approval is granted by the CPHS.
- E. Specimens and data prospectively collected for pre-defined research purposes that is limited to a single CPHS approved proposal are not appropriate for a research repository.

Retrospective use of previously collected or stored specimens for research dictates a choice of either anonymous samples which contain no subject identifier, or samples which can be identified by the PI or a third party.

The NBSR is the custodian of biological specimens and serves as a source of data and specimens for future research studies.

3. Technical and Operational Guidelines

The NBSR has been established to maintain a specimen collection for study of human spaceflight-related changes. The repository supports the Human Research Program, which is charged with identifying and investigating physiological changes that occur during human spaceflight, and developing and implementing effective countermeasures when necessary. Investigators should consult with the director of the NBSR to insure compliance with requirements for specimen collection and storage. All protocols for specimen collection require CPHS review and approval as well as written informed consent from the subject. Each new use of a specimen or data must have CPHS approval.

3.1. Specimen Collection, Processing, Storage, and Retrieval (Eiseman, ISBER, NCAB)

3.1.1. Collection

Specimens may be obtained from astronauts, other space flight participants and control subjects. Sample acquisition may include blood from venipuncture or fingerstick, urine collections, and tissue biopsy. Specimens may include, but are not limited to, blood, urine, saliva, and buccal cells, and tissue. It is anticipated that multiple specimens and data from a subject will be collected over a period of time. Approved specimens may be submitted in either identified or de-identified status. The repository will track research requests, guide the collection and storage process, and implement new methodologies as appropriate.

Specimens that are submitted to the NBSR must include appropriate documentation. The following guidelines should be met:

All samples:-

- A. Specimen annotation and recording of key data (e.g. time to freezing, character of chemical preservation, time of fixation if tissue specimens are excised, or other special information that may be needed) must be included.
- B. Blood specimen data recording must include the following:
 - 1) Collection time relative to treatment or other interventions
 - 2) Time of day or mission elapsed time at collection
 - 3) Subject's fasting status
 - 4) Position of subject during collection

Identified samples: name, sex, ground or spaceflight sample (mission identification); part of another test

The principal investigator must:

- A. Specify whether data is attributable or not attributable

- B. Certify that risks been explained in consent form

3.1.2. Processing

Special processing of biological specimens may include:

- A. Division of individual specimens into aliquots or fractions whenever possible; with consideration given to vial size, number of vials for typical aliquots, anticipated investigator uses, and number of investigators.
- B. Long term storage of all blood components if practical and procedures to maximize availability of specimens for other distribution and research.
- C. Optimal processing to preserve the greatest number of analytes possible (e.g. freezing, fixation, use of stabilizing additives) unless alternate processing is required for a specific study.
- D. Additional steps to protect confidentiality required if permanent cell lines will be established or if DNA will be extracted
- E. A quality management system to ensure adherence to standards.

3.1.3. Storage

Specimen storage guidelines incorporate the following:

- A. Standard bar code unique identifier for each specimen aliquot, with all other relevant information tied solely to the identifier
- B. Storage temperatures less than -40C
- C. Avoidance of unnecessary thawing and refreezing of frozen specimens
- D. Separation of liquid specimen components, such as blood and urine, before storage whenever possible, to facilitate preservation of each constituent under specific optimal conditions.
- E. Use of inventory tracking to minimize disruption of the stable environment during sample retrieval
- F. Automated security systems to continuously monitor the function of storage equipment.
- G. Emergency procedures for protection of specimens for environmental, electrical, and equipment failures
- H. An empty, functioning freezer as back-up for of single-freezer failure

3.1.4. Specimen Retrieval (including transport and shipment)

The following guidelines apply to specimen retrieval, transport, and shipment:

- A. Use of an approved, standard checklist during specimen retrieval and documentation of deviations from storage parameters.

- B. Bar codes to document retrieval of specimens for transport.
- C. Air transport, packaging and labeling to conform to International Air Transport Association (IATA) regulations.
- D. Temperature recorder during transport
- E. Appropriate insulation, such as gel packs conditioned for refrigerated or frozen temperatures
- F. Standardized paperwork accompanying shipments including shipping manifest, list of sample identification numbers, and sample descriptions

3.2. Collection and Management of Clinical Data

NBSR has established a standardized set of common data elements for all specimens, including but not limited to, demographic, mission-associated data, and mission-specific information.

3.3. Collection of Longitudinal Clinical Data

NBSR maintains all relevant longitudinal clinical data associated with a specimen. This will maximize the use of specimens for current and future studies, both short-term and long-term. Participating investigators must annotate each specimen.

Following informed consent from the subject, NSBR obtains identifying and contact information from the Flight Medicine Clinic and the Longitudinal Study of Astronaut Health offices.

Information linked to specimens may include demographic data, environmental and occupational exposures, and additional diagnostic studies.

4. Repository

4.1. General Informatics Guidelines:

The system must be searchable with variable levels of access for different individuals. Permissions and user roles should be defined to ensure proper access to data and specimens in compliance with CPHS policies and Federal regulation.

Research design must include protection for the privacy of individuals who contribute specimens to repositories. It must maintain the confidentiality of associated clinical data and other private information. Because many confidentiality issues arise in the context of research using medical records and biological specimens, there should be a single system of protection for both types of research.

Use of specimens from the repository is restricted to the authorization granted by the subject in the original consent form that was used to procure the specimen, unless (1) the sample is studied without identifiers or, (2) additional consent for a CPHS approved protocol has been obtained from the specimen donor. Such consent must be obtained using an updated informed consent document that has been approved by the CPHS.

The repository will collect, store, and distribute human biological specimens for multiple researchers with separate research projects. It has not been established to provide customized services for individual researchers.

4.2. Specimen Tracking, Inventory Control, and Data Management (Eiseman, NCAB)

4.2.1. Specimen Tracking

Each specimen is assigned a unique identifier (number and barcode) at the time of collection. The identifier links the information it contains to the labeled specimen containers. (See section 3.1.3.A). Specific clinical and epidemiological data is identified by the same number and barcode. The informatics system tracks clinical data associated with a specimen and permits collection of common data elements. Standardized data-entry forms must be used. The same number or code is used to track specimens from collection through processing, storage, and distribution.

4.2.2. Repository Inventory Control and Data Management

The repository databases must be updated each time any specimen is moved within or out of the repository. The inventory system must be able to track the actual flow of information, specimens, and data into, within, and out of the system. There must be definition of procedures by which specimens are de-linked from subject identities (i.e. when is the de-linking performed, who performs de-linking, what identifying information is removed, and how).

These NASA repository databases must be located in a secure site monitored by the institution and use a data access system with clearly defined levels of access privileges. These access levels are described in the protocol for operation of the repository as well as in the informed consent form approved by CPHS. Repository policies address access to subject identities and the protection of personally identifiable information related to the sample. The number of personnel allowed access to links and identity information must be kept to a minimum and access must be appropriately monitored to ensure compliance.

Policies governing records and specimen retention include the following:

- A. Procedures for handling and disposition of specimens and associated data at one or more of the following points: (1) completion of the specific research objectives of the study, (2) depletion of specimens, or (3) achievement of critical data endpoints.
- B. Ensuring that subjects who contribute specimens and/or data for research purposes are fully informed that research done with these specimens may help to develop products, tests, or discoveries that may have commercial value and that they, the subject, may not receive any direct benefit or royalty from such discoveries.
- C. Agreement signed by the requesting investigator that he/she will abide by all the rules of the NBSR including the return of unused portions of specimens to the repository prior to release of the specimens.

4.2.3. Paper Documents

Paper documents may include consent forms, such as research protocol consents and the consents specifically for specimen repository. All paper documents must be maintained in locked, secure storage cabinets.

4.3 Information Technology (IT) Security

All researchers who collect, use, or distribute health-related data must adhere to IT security policies. IT security includes the following:

- A. Physical protection of hardware and data.
- B. Electronic protection of records stored on servers, workstations, and portable electronic devices.
- C. Protection of data transmitted via electronic means such as e-mail, wireless, or internet servers.
- D. Policies and procedures for both the physical and electronic security of systems that contain electronic health-related data.

The repository must be able to recover its inventory data that may be lost due to physical destruction (fire, hurricane) or due to electronic hacking. The recovery backup system must be kept physically separate from the database at offsite storage and must be tested for reliability before an emergency.

4.4 Repository Quality Assurance (QA)/Quality Control (QC)

The NASA repository has a QA/QC program to monitor and evaluate the quality and appropriateness of the services provided. The program uses systematic ongoing monitors that identify important aspects of care unique to the repository. The program defines indicators with specific thresholds used for monitoring and evaluating all functional areas of the repository. When the thresholds are crossed, then appropriate action can be taken to improve the quality of service.

The repository falls under the stewardship of the JSC Clinical Laboratories, which maintain certifications from the College of American Pathologists (CAP) and under Clinical Laboratory Improvement Amendments (CLIA). Each employee will receive training in relevant areas of safety before beginning work and this training will be updated annually.

4.5 Biohazard Precautions

Repository work practices are based on universal precautions and practices similar to the practices of clinical laboratories. The repository operates under OSHA "Occupational Exposure to Blood borne Pathogens", 29 CFR 1910.1030(d)(3)) (56 FR 64175). Furthermore, NASA offers immunization to employees to protect them from vaccine-preventable diseases (NASA NPR 1800.1.A).

Human specimens are handled in accord with Biosafety Level 2 (BSL-2) as outlined in the Centers for Disease Control and Prevention (CDC) booklet *Biosafety in Microbiological and Biomedical Laboratories* (CDC and NIH 1999). Under BSL-2, when specimen containers are opened for processing, they are handled in a BSL-2 biological safety cabinet (hood). High-risk specimens (BSL-3 and 4) are excluded from the repository.

5. Informed Consent, Legal, and Policy Guidelines

5.1 Informed Consent

Informed consent must provide a potential human research subject with sufficient information, including anticipated procedures, risks, and benefits, to allow the subject to make a fully informed decision whether or not to participate in the research protocol. Informed consent for the donation of biological specimens to the repository must be secured separately from consent to the use of these specimens in specific research studies.

NASA biomedical research regulations must be in agreement with the Common Rule and the HIPAA Privacy Rule (NASA Memo reference). The CPHS requires the consent form to include information regarding sample storage and provide the subject with full information of possible uses.

Obtaining informed consent for collection and storage of biological specimens and for their use in future studies is challenging, since details of the future research may not be known at the time the specimen is collected. For example, a specific use may be considered to be ‘studies related to space flight physiology’ or ‘bone studies’. The more sensitive the data to be released, the more description the CPHS requires. Thus, the statement ‘future genetic research’ would not be acceptable. In general, a subject cannot meaningfully consent to an unspecified use of a donated specimen. Subjects should be provided with the information of possible future use of their samples. When new uses are proposed which have not been described to them in a previously signed informed consent statement, the subject must sign an additional consent form because new uses may present new risks as well as privacy concerns. If specimens are stored without personal identification, future use does not have to be specifically described in the consent.

5.1.1 Standard Consent Template

Standard consent template must include:

- A. Type of specimen(s) the subject is to donate (e.g. blood, urine, or tissue)
- B. Types of research for which the specimens may be used, including broad use of specimens (e.g. a specific research project, general research, or genetic research)
- C. Anonymous versus coded specimen storage (if the latter, the consent should include language as to why the identity is required)
- D. Whether the participant’s medical records can be accessed, what type of information is sought, and the duration of access to medical records
- E. List of specific restrictions for specimen usage (see tiered consent below)
- F. Description of planned future specimen usage (if future usage is unknown, it should be so stated in the consent document)
- G. Description of the procedures for protecting the privacy of subjects and maintaining confidentiality of data
- H. Information regarding the control and ownership of the specimens during storage i.e. all specimens shall belong to NASA.
- I. Clarification of the rights of the participants including the right to withdraw his/her consent at any time either by requesting that the specimen be destroyed or that all personal identifiers be removed

- J. Expected timeframe of specimen storage
- K. Subject's access to stored samples particularly when that information may be of clinical relevance to him/her (if such information will not be available in the future [e.g. because personal identifiers are to be removed] the consent form should clearly state this)
- L. List all other approved co-investigators and their affiliations who will have access to specimens and data (e.g. in-house researchers only, other academic collaborators, industry sponsor). All future third-party access requests must come through the NBSR and the CPHS.
- M. Possible secondary use of the stored specimen
- N. Statement that specimens may be used in the development of tests, products or discoveries that may have potential commercial value and that subjects will not be paid or receive money.

5.1.2 Tiered Consent

Donor subjects must be offered options over the scope of use (known as tiered consent) (Eiseman), thus permitting:

- A. Only unidentified or unlinked use of their biological samples in research
- B. Coded or identified use of their biological samples for one particular study only, with no further contact permitted to request permission for future studies (opt-out)
- C. Coded or identified use of biological samples for one particular study only, with further contact permitted to ask for permission for future studies
- D. Coded or identified use of biological samples for any study relating to the condition for which the sample was originally collected, with no further contact allowed to seek permission for other types of studies
- E. Coded or identified use of biological samples for any study related to the condition for which the sample was collected, with further contact allowed to request permission for other studies.
- F. Commercial use of biological samples
- G. Sharing of their biological samples with other investigators without specific re-consent (NBAC) in which above conditions apply.

5.1.3 Protocol Elements

In addition to all of the elements listed in the above informed consent section, the following should be included in the protocol submitted to the CPHS for review:

- A. Type of samples to be used in the study (anonymized, unlinked, coded, or identified)
- B. General descriptions of tests that will be performed on the samples

- C. Full description of the mechanisms used to link specimens and identifiable information, and procedures used to maximize the protection against inadvertent release of confidential information
- D. Verification from repository review of each informed consent that this is an acceptable use of the sample.
- E. Verification that the use of samples from the repository will be restricted to the stipulations indicated in the original consent form used to procure the specimen.

5.2 Genetic Privacy

The risks of genetic screening and testing are primarily psychosocial but may also include financial, insurability and other issues. Genetic screening and testing require justification in terms of their probable benefits, which vary from genetic condition to condition. These risks will also be affected by whether the screening and testing are for active disease or disposing condition/ carrier status, whether preventive or treatment measures are available, and whether the information is important for reproductive decisions. For any genetic screening or testing, fundamental questions concern who will use the resulting information, how they will use it and for what purposes (Beauchamp).

A separate application will be necessary for investigators using de-identified data or specimens for genetic research. Tissue or information in the database may only be used within the parameters of the informed consent form. CPHS will determine if additional consent from the subject is required to conduct the research.

Research which involves a genetic component must address the following concerns:

- A. Ability to detect markers of previously undiagnosed or unrecognized illnesses, or susceptibility to physiologic changes and illness, over time
- B. Explanation in the consent form of how subjects will be informed that they have a right to be notified (or not) about the results, and whether or not genetic counseling is available.
- C. Attempts by employers and insurers to gain access to research data, specifically for the purpose of denying employment, denying insurance, or rating insurance higher
- D. Commercial developments involving stored specimens
- E. Use of stored samples for research.

5.3 Withdrawal of consent

NASA will develop procedures to handle specimens and associated database records for which consent has been withdrawn. In the event that consent is withdrawn, the specimen, data, and electronic records will be removed from the repository if the specimen retains identifiers to link it to that individual. Any distributed sample may be returned to the repository, but a processed sample and the research data generated from it cannot be rescinded. In the event that consent is withdrawn, specimens must be destroyed. If, however, the specimen has been stripped of identifiers so that the link back to the identity of the tissue source has been destroyed, it is not possible to identify the tissue to withdraw it from the repository.

5.4 Disclosure of research results

In some cases, research will yield results that could affect the medical care of some subjects. In these instances, it may be appropriate to tell subjects that they may choose to receive the results. However, if the research is in the early stages and clinical significance has not been established, it may be unethical to provide results to subjects. Likewise, it would be inappropriate to disclose research results to subjects who have specifically stated they do not want the results. Participants will be asked to indicate their preferences regarding receiving research results (Wolf).

Such disclosures should occur only when all of the following apply:

- A. Findings are scientifically valid and confirmed
- B. Findings have significant implications for the subject's health concerns, and
- C. Course of action to ameliorate or treat these concerns is readily available (Appendix 2, NBAC rec. 14).
- D. The individual requests the information.

Investigators will be asked to describe anticipated research findings and circumstances that might lead to disclosure of the research findings to the subject. The investigator should identify how they will communicate information to the subject, the family, or a health care provider (Wolf, Appendix 1, NBAC rec. 15, 16).

5.5 Confidentiality

Steps to protect confidentiality include:

- A. Coded specimens with identifiers in password-protected databases
- B. Limited access to identifiers and other data
- C. Specimens stripped of identifiers (anonymized), where possible

6.0 Access to and Distribution of Specimens and Data

6.1. Guidelines

As the NASA community's steward of specimens, the NBSR will establish guidelines for sample distribution and clinical data sharing that are consistent with ethical principles, prevailing laws and regulations, intellectual property policies, and consent form language. CPHS or a CPHS advisory board will evaluate each request by an investigator for use of samples to insure the request is consistent with both CPHS conditions for sharing samples and with the original and revised informed consent.

6.2 Access and Distribution

Specimen access and distribution practices must reflect the mission of the NBSR. The prioritization system for specimen distribution requires a prescribed mechanism for review of requests, to include the following:

- A. A peer review system that determines priorities for allocation of specimens to qualified investigators
- B. Preference for access will be given to investigators for space flight studies directly related to the NASA mission before access is granted to other investigators.
- C. Scientific merit of the research proposal, with attention to research design, scientific and programmatic relevance, and likelihood that the research will provide meaningful results
- D. Strong scientific rationale in research plan to justify use of rare, limited resource specimens
- E. Proven investigator experience with the method proposed
- F. Statistical evaluation which shows that the number of samples requested are adequate to meet the stated aims
- G. Definition of a study interval and information about the research outcome at the end of the period
- H. Agreement by the investigator to make all data freely available to NASA and its designees (and to publish de-identified data so others may have access to the information.)
- I. Assurance that proposed uses are consistent with subjects' consent, research purpose, and allowable use of specimens
- J. Policies to control the distribution of rare specimens
- K. Control over the last sample of a particular specimen
- L. Prevention of the control of an entire specimen or type of specimen by one researcher
- M. Investigator agreement covering confidentiality, use, disposition, and security of specimens and associated data
- N. Investigator agreement in writing covering publication and sharing of research results, and ownership of future intellectual property
- O. Funding level for project and CPHS approval for such funding allocation
- P. Types of associated data, including identifiers, to be provided with the specimen
- Q. Control of the secondary distribution of specimens (policy that forbids investigator from transferring specimens to third party)
- R. Establishment of an appeals process addressing disputes over allocation decisions

6.3 Investigator duties

Investigators must provide the following to the NBSR:

- A. Separate CPHS approval of each specific research project that uses data and specimens from the repository
- B. IRB approval from the investigator's home institution
- C. Written informed consent from each participant when the extracted data will contain personal identifiers
- D. Report of their research results and all data obtained
- E. Transfer of their collection to NBSR upon separating from NASA , at the completion of the approved studies, or at any time required by the NBSR

6.4 Intellectual Property

Inventions arising from research using specimens from NBSR may have commercial value. Courts have ruled that individuals have no rights to own or control biological materials that they have contributed for research purposes, even if the research leads to new products. The NBSR will maintain control over specimens, associated data, and research findings by applying intellectual property rights. Material Transfer Agreements must be implemented before distributing specimens from the NBSR.

The NBSR will ensure:

- A. Research data from repository specimens are made available to the NASA research community
- B. Specimens will be used only for the purposed cited in the application and no specimens will be shared with a third party without the prior written permission of the repository (Eiseman)

APPENDIX 1

Research Using Human Biological Specimens

- A1.1. Policy on Use of Prospectively Collected Specimens for Research Repository**
- A1.2. Policy on De-identified and Coded Specimens**
- A1.3. Policy on Use of Existing Collections of Specimens in Retrospective Research**
- A1.4. Policy on Conversion of a Clinical Database/Repository to a Research Database/Repository**
- A1.5. Policy on Conversion of a Research Study Protocol to a Research Database/Repository Protocol**
- A1.6. Policy on Waiver of Informed Consent for Use of Stored Specimens**

Issues of de-identification, confidentiality protection, and appropriate consent procedures with respect to these studies are not straightforward, in part because the Common Rule, the Privacy Act of 1974 as amended, and HIPAA differ with respect to what subjects must be told about the future uses of their samples when they agree to participate in specimen collection, storage, and/or use studies. For example, although the Common Rule would allow broader future use of stored specimens, HIPAA requires that future use be specific. As such, subjects must be provided with specific information regarding the future use of their specimens if their samples are identifiable and such information must be included in the informed consent. For studies which involve de-identified specimens, this issue does not apply. De-identified specimens may be used for broader purposes with appropriate CPHS approval.

Appendix 1.1. Policy on Use of Prospectively Collected Specimens for Research Repository (see Appendix 2, NBAC rec. 9)

A1.1.1 The prospective collection of specimens for a repository for studies which involve the storage of identifiable samples must provide subjects either:

- A. Specific information about how their samples might be used in the future
- OR-**
- B. A subsequent informed consent when new uses are proposed for their samples that had not been previously described to them in their signed informed consent statement

Depending on the circumstances of the study, subjects must be given the right to consent to specific use of their sample, rather than providing consent to unspecified research.

A1.1.2 If prospectively collected specimens are de-identified and have no link to the identifier, no written informed consent from the specimen donor is required and the specimens may be used for unspecified research.

A1.1.3 All research on prospectively collected specimens must meet the following requirements:

- A. Protocols and consent forms must have CPHS approval before subjects are contacted.
- B. All plans to store specimens from a given protocol for future research use, must be specified, justified and included in the consent form.

- C. If the proposed research falls outside the uses specified in an original consent form, the investigator will need to re-consent all of the donors before their specimens can be used in this or any subsequent study.
- D. Any study proposing to collect specimens using procedures that pose greater than minimal risk to subjects requires full review by CPHS. Protocols vary widely and may include specimen banking for future research. Examples include:
 - a. Specimens that will be collected as part of a larger protocol such as an intervention study and involving treatments or procedures that are more invasive than a routine blood draw generally have more than minimal risks.
 - b. Greater than minimal risk procedures will be used to obtain additional specimens, i.e. materials in excess of that required for diagnosis or treatment.

Appendix 1.2. Policy on De-identified and Coded Specimens (see Appendix 2, NBAC rec. 1, 3, 4)

- 1.2.1 According to recent guidance from OHRP, the human subject definition does not apply to research involving de-identified (anonymized) specimens. However, research conducted with unlinked (coded) samples is human subject research and is regulated by the Common Rule [45CFR46.101(b)(4) or 45CFR46.102(f)]. At NASA, CPHS determines whether research involves human subjects and assesses the study procedures to ensure that the specimens are either (1) de-identified or, (2) coded, with adequate subject privacy protection measures in place.
- 1.2.2 A de-identified data set may include a tracking code or other numbering system, provided that:
 - A. The tracking code is not derived from or related to information about the individual.
 - B. The re-identification algorithm is not disclosed to the data recipient.
- 1.2.3 Investigators may create unlinked (anonymized) samples from coded or identified materials already in the repository, by ensuring that:
 - A. The process used to unlink the samples will be effective
 - B. The unlinking of the samples will not unnecessarily reduce the value of the research
 - C. The key to decipher the code is destroyed before the research begins
- 1.2.4 In some cases, an investigator who obtains unlinked coded private information or specimens may unexpectedly learn the identity of one or more individuals, or for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained information or specimens pertain, he/she must immediately notify the NBSR and the CPHS. The research activity would require CPHS review of the research and informed consent from the subject(s).

- 1.2.5 When identifiers are retained by the NBSR, a limited coded data set may be extracted for the investigator to meet research goals. Before releasing coded and/or identified samples from its collection, the repository will require that the investigator provide documentation from the CPHS that the research will be conducted in compliance with applicable NASA and other federal regulations.
- 1.2.6 Prospective collection of coded or identified samples for databases/repositories must be obtained using written consent. If the biological specimens can be linked to identifiers that are known to the research team, written informed consent is required.

Appendix 1:3. Policy on Use of Existing Collections of Specimens in Retrospective Research (see Appendix 2, NBAC rec. 4, 8)

New studies using previously stored specimens, whether collected for clinical or research purposes, must obtain CPHS approval. The level of review depends on the following:

- A. If samples are to be used in a de-identified manner, (without linkage to subject identifiers), no written informed consent or documentation of Privacy Rule authorization of waiver is required.
- B. If the subject donors did not give explicit consent for future use of biological samples, investigators may use those materials for research only if the materials are permanently stripped of identifiers.
- C. If samples can be linked to identifiers either by the principal investigator or a third party, then, depending on the nature of the protocol, investigators are required to obtain informed consent from the subjects for the new use.
- D. Subjects may be contacted for permission to use their past data and/or specimens for research purposes. The usual CPHS procedures must be followed by having a CPHS-approved protocol and strategy for obtaining informed consent.

Appendix 1:4. Policy on Conversion of a Clinical Database/Repository to a Research Database/Repository (see Appendix 2, NBAC rec. 6, 7, 10, 11, 12)

1.4.1. Data/specimens that have been stored in a database/repository solely for clinical or diagnostic purposes in the past can be moved into a research database/repository under a CPHS waiver of informed consent provided the federal criteria for waiver of consent [45CFR46.116(d)] and waiver of authorization 45CFR164.512(i)(1)and(2)] are met. The principal requirements for waiver are:

- A. No more than minimum risk
- AND-
- B. No adverse effect on rights or welfare
- AND-
- C. Research cannot “practicably be carried out” without the waiver.

NOTE: At the present time there is no specific federal guidance for defining “practicably.” Practicably in some institutions has been interpreted to mean that informed consent can be waived for use of data and specimens from patients who have been seen in the past, but

who are not expected to be seen on a regular and frequent basis in the future. This is not the case for most subjects at JSC. Subjects who are expected to return soon should be asked for written informed consent for use of their clinical specimens at their next visit.

NOTE: Research that poses greater than minimal risk to subjects, that is collection of private information and/or collection of specimens by more invasive means than a blood draw, require full review by CPHS.

- 1.4.2. Written informed consent to the research use of human biological specimens must be obtained separately from informed consent to clinical procedures. The person who obtains informed consent in these clinical settings must make clear to the potential subjects that their refusal to consent to the research use of their biological specimens will in no way affect the quality of their clinical care.

Appendix 1:5. Policy on Conversion of a Research Study Protocol to a Research Database/Repository Protocol (see Appendix 2, NBAC rec. 6, 8, 12)

- 1.5.1. When a research database/repository is established for use in future studies, the protocol should be split into a separate protocol for the specific study and for the database/repository, with distinct informed consent forms. This is primarily a paperwork activity to reword the protocol summaries and informed consent forms to meet the requirements outlined above. Subjects who are currently enrolled under the combined protocol usually will not have to be re-consented because they have already given informed consent for both the specific study and the database/repository. Future subjects in the research study must sign separate informed consent forms for both the specific study and the database/repository.
- 1.5.2 Another type of collection is comprised of those specimens collected by individual investigators and not originally intended to be shared with others, but which are subsequently shared as part of a repository. Any collection may be considered a repository if it contains specimens that are potentially identifiable and are distributed to someone other than the principal investigator (or, in the case of a multi-investigator study, other than any of the identified investigators). Investigators and the CPHS must review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped so that the samples are unlinked (Appendix 2, NBAC rec. 8).
- 1.5.3 A waiver of informed consent can be granted by the CPHS for inclusion of data and specimens that have been collected from individuals who participated in past research studies. Research using existing specimens (clinical or research) must meet the federal criteria for waiver of consent [45CFR46.116(d)] and waiver of authorization [45CFR164.512(i)(1)and(2)]. (See Appendix 1.4.1, A-C.)

Appendix 1.6. Policy on Waiver of Informed Consent for Use of Stored Specimens (see Appendix 2, NBAC rec. 10, 11, 12)

- 1.6.1 The CPHS will consider waiver of informed consent based upon the federal criteria for waiver of consent [45CFR46.116(d)] and waiver of authorization [45CFR164.512(i)(1)and(2)]. (See Appendix 1.4.1, A-C.)

1.6.2 Research on coded samples is of minimal risk to the subject if (Appendix 2, NBAC rec. 10):

- A. The study adequately protects the confidentiality of personally identifiable information obtained in the course of research,
- B. The study does not involve the inappropriate release of information to third parties
-AND-
- C. The study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.

1.6.3 In determining whether a waiver of consent would adversely affect a subject's rights and welfare, the CPHS should consider:

- A. If the waiver would violate any state or federal regulation or customary practice regarding entitlement to privacy or confidentiality,
- B. If the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects

1.6.4 Assurance that all data and specimens exist at the time of the CPHS request for waiver: The PI must give written assurance in the protocol summary that only existing data and specimens will be used, and that those data and specimens will be only those that were collected during a time period between two specified dates in the past. This includes data and specimens that have been collected in the past from individuals for other research studies or solely for clinical purposes. Waiver of informed consent for use of existing data and specimens will be approved only once per research use because care must be taken to ensure that the waiver is granted only for data and specimens that are "on the shelf" at the time of the waiver request. The continued collection of such data/specimens must occur solely for non-research purposes.

1.6.5 Sensitivity of data and specimens: Informed consent should not be waived for use of data or specimens that are potentially highly sensitive and are linked to patient identifiers, e.g., data on major psychiatric diagnoses and specimens for studies that could produce genetic information with potentially damaging consequences.

1.6.6 Previous informed consent given for use of data and specimens in research: Consideration will be given for waiver of informed consent related to specific studies in which the subjects have already given informed consent for storage of the data and specimens in a research database/repository and for their use in future research related to the area of research covered by database/repository.

1.6.7 Specimens banked for future research cannot be waived under this exemption policy.

APPENDIX 2

National Bioethics Advisory Commission (NBAC) on Research Involving Human Biological Materials: Ethical Issues and Policy Guidance http://www.georgetown.edu/research/nrcbl/nbac/hbm_exec.pdf

Recommendations (excerpted from NBAC)

[Note 1: Office for Protection from Research Risks (OPRR) became the Office of Human Research Protections (OHRP) within the Department of Health and Human Services (DHHS), effective June 2000]

[Note 2: HIPAA rules were released following this guidance and may be more restrictive.]

Interpretation of the Existing Federal Regulations

NBAC offers the following recommendations to improve the interpretation and implementation of the existing federal regulations as they apply to research using human biological materials.

Recommendation 1:

Federal regulations governing human subjects research (45 CFR 46) that apply to research involving human biological materials should be interpreted by the Office for Protection from Research Risks (OPRR), other federal agencies that are signatories to the Common Rule, IRBs, investigators, and others, in the following specific ways:

- a) **Research conducted with unidentified samples is not human subjects research and is not regulated by the Common Rule.**
- b) **Research conducted with unlinked samples is research on human subjects and is regulated by the Common Rule, but is eligible for exemption from IRB review pursuant to 45 CFR 46.101(b)(4).**
- c) **Research conducted with coded or identified samples is research on human subjects and regulated by the Common Rule. It is not eligible for exemption unless the specimens or the samples are publicly available as defined by 45 CFR 46.101 (b)(4). Few collections of human biological materials are publicly available, although many are available to qualified researchers at reasonable cost. Therefore, OPRR should make clear in its guidance that in most cases this exemption does not apply to research using human biological materials.**

The current federal regulations appear to make eligible for expedited review, 1) research on materials that will be collected for clinical purposes or, 2) those that will be collected in noninvasive or minimally invasive ways for research purposes. NBAC finds that there is no need to distinguish between collections originally created for clinical purposes and those created for research purposes. In both cases, research on the collected materials should be eligible for expedited review if the research presents no more than a minimal risk to the study subjects. (See the discussion of minimal risk below.)

Recommendation 2:

OPRR should revise its guidance to make clear that all minimal-risk research involving human biological materials—regardless of how they were collected—should be eligible for expedited IRB review.

Special Concerns About the Use of Unlinked Samples

Given the importance of society's interest in treating disease and developing new therapies, a policy that severely restricts research access to unidentified and unlinked samples would severely hamper research and could waste a valuable research resource. As noted in Recommendation 1, research using unlinked samples may be exempt from review. However, if coded or identified samples are rendered unlinked by the investigator, special precautions are in order.

Recommendation 3:

When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, an IRB (or other designated officials at the investigator's institution) may exempt the research from IRB review if it determines that

- a) the process used to unlink the samples will be effective, and**
- b) the unlinking of the samples will not unnecessarily reduce the value of the research.**

Requirements for Investigators Using Coded or Identified Samples

Repositories and IRBs share responsibility with investigators to ensure that research is designed and conducted in a manner that appropriately protects human subjects from unwarranted harms.

Recommendation 4:

Before releasing coded and/or identified samples from its collection, a repository should require that the investigator requesting the samples either provide documentation from the investigator's IRB that the research will be conducted in compliance with applicable federal regulations or explain in writing why the research is not subject to those regulations.

Recommendation 5:

When reviewing and approving a protocol for research on human biological materials, IRBs should require the investigator to set forth

- a) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects,**
- b) a full description of the process by which samples will be obtained,**
- c) any plans to obtain access to the medical records of the subjects, and**
- d) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.**

When an investigator obtains access to a patient's medical records, either to identify sample sources or to gather additional medical information, human subjects research is being conducted. IRBs should adopt policies to govern such research, consistent with existing OPRR guidance related to medical records research.

Obtaining Informed Consent

Research using coded or identified samples requires the consent of the source, unless the criteria for a consent waiver have been satisfied. Unfortunately, the consent obtained at the time the specimen was obtained may not always be adequate to satisfy this requirement. When research is contemplated using existing samples, the expressed wishes of the individuals who provided the materials must be respected. Where informed consent documents exist, they may indicate whether

individuals wanted their sample to be used in future research and in some instances may specify the type of research.

When human biological materials are collected, whether in a research or clinical setting, it is appropriate to ask subjects for their consent to future use of their samples, even in cases where such uses are at the time unknown. In this latter case, however, particular considerations are needed to determine whether to honor prospective wishes.

Whether obtaining consent to the research use of human biological materials in a research or clinical setting, and whether the consent is new or renewed, efforts should be made to be as explicit as possible about the uses to which the material might be put and whether it is possible that the research might be conducted in such a way that the individual could be identified. Obviously, different conditions will exist for different research protocols, in different settings, and among individuals. NBAC notes that the current debate about the appropriate use of millions of stored specimens endures because of the uncertain nature of past consents. Investigators and others who collected and stored human biological materials now have the opportunity to correct past inadequacies by obtaining more specific and clearly understood informed consent.

Recommendation 6:

When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent to clinical procedures.

Recommendation 7:

The person who obtains informed consent in clinical settings should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.

Recommendation 8:

When an investigator is conducting research on coded or identified samples obtained prior to the implementation of NBAC's recommendations, general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time. Investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped so that samples are unlinked.

Recommendation 9:

To facilitate collection, storage, and appropriate use of human biological materials in the future, consent forms should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make. Such options might include, for example:

- a) refusing use of their biological materials in research,**
- b) permitting only unidentified or unlinked use of their biological materials in research,**
- c) permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies,**
- d) permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies,**

e) permitting coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, or

f) permitting coded use of their biological materials for any kind of future study.*

Criteria for Waiver of Consent

When an investigator proposes to conduct research with coded or identified samples, it is considered to be research with human subjects. Ordinarily the potential research subject is asked whether he or she agrees to participate. Seeking this consent demonstrates respect for the person's right to choose whether to cooperate with the scientific enterprise, and it permits individuals to protect themselves against unwanted or risky invasions of privacy. But informed consent is merely one aspect of human subjects protection. It is an adjunct to—rather than a substitute for—IRB review to determine if the risks of a study are minimized and acceptable in relation to its benefits.

When a study is of minimal risk, informed consent is no longer needed by a subject as a form of self-protection against research harms. However, it is still appropriate to seek consent in order to show respect for the subject, unless it is impracticable to locate him or her in order to obtain it. Thus, when important research poses little or no risk to subjects whose consent would be difficult or impossible to obtain, it is appropriate to waive the consent requirement.

Recommendation 10:

IRBs should operate on the presumption that research on coded samples is of minimal risk to the human subject if

- a) the study adequately protects the confidentiality of personally identifiable information obtained in the course of research,**
- b) the study does not involve the inappropriate release of information to third parties, and**
- c) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.**

Failure to obtain informed consent may adversely affect the rights and welfare of subjects in two basic ways. First, the subject may be improperly denied the opportunity to choose whether to assume the risks that the research presents, and second, the subject may be harmed or wronged as a result of his or her involvement in research to which he or she has not consented. Further, when state or federal law, or customary practice, gives subjects a right to refuse to have their biological materials used in research, then a consent waiver would affect their rights adversely. Medical records privacy statutes currently in place or under consideration generally allow for unconsented research use and could be interpreted to suggest a similar standard for research using human biological materials. But as new statutes are enacted, it is possible that subjects will be given explicit rights to limit access to their biological materials.

Recommendation 11:

In determining whether a waiver of consent would adversely affect subjects' rights and welfare, IRBs should be certain to consider

- a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality,**
- b) whether the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects, and**

c) whether the study's results might adversely affect the welfare of the subject's community.

Even when research poses no more than minimal risk and a consent waiver would not affect the rights and welfare of subjects, respect for subjects requires that their consent be sought. However, on some occasions, demonstrating this respect through consent requirements could completely halt important research. An investigator who requests a waiver of the informed consent requirement for research use of human biological materials under the current federal regulations must provide to the IRB evidence that it is not practicable to obtain consent. Unfortunately, neither the regulations nor OPRR offers any guidance on what defines practicability.

Recommendation 12:

If research using existing coded or identified human biological materials is determined to present minimal risk, IRBs may presume that it would be impracticable to meet the consent requirement (45 CFR 46.116(d)(3)). This interpretation of the regulations applies only to the use of human biological materials collected before the adoption of the recommendations contained in this report (specifically Recommendations 6 through 9 regarding informed consent). Materials collected after that point must be obtained according to the recommended informed consent process and, therefore, IRBs should apply their usual standards for the practicability requirement.

NBAC recognizes that if its recommendation that coded samples be treated as though they are identifiable is adopted, there may be an increase in the number of research protocols that will require IRB review. If, however, such protocols are then determined by an IRB to present minimal risk to a subject's rights and welfare, the requirement for consent may be waived if the practicability requirement is revised for this category of research. However, it must be noted that by dropping the requirement that consent must be obtained if practicable, NBAC does so with the expectation that the process and content of informed consent for the collection of new specimens will be explicit regarding the intentions of the subjects and the research use of their materials. (See Recommendations 6 through 9 concerning informed consent.)

According to current regulations, the fourth condition for the waiver of consent stipulates that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45CFR 46.116(d)(4)). Thus, according to the regulations, an IRB, while waiving consent (by finding and documenting the first three required conditions), could require that subjects be informed that they were subjects of research and that they be provided details of the study—a so-called debriefing requirement. In general, NBAC concludes that this fourth criterion for waiver of consent is not relevant to research using human biological materials and, in fact, might be harmful if it forced investigators to recontact individuals who might not have been aware that their materials were being used in research.

Recommendation 13:

OPRR should make clear to investigators and IRBs that the fourth criterion for waiver, that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45CFR 46.116(d)(4)), usually does not apply to research using human biological materials.

Reporting Research Results to Subjects

Experts disagree about whether findings from research should be communicated to subjects. However, most do believe that such findings should not be conveyed to subjects unless they are confirmed and reliable and constitute clinically significant or scientifically relevant information.

Recommendation 14:

IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following apply:

- a) the findings are scientifically valid and confirmed,**
- b) the findings have significant implications for the subject's health concerns, and**
- c) a course of action to ameliorate or treat these concerns is readily available.**

Recommendation 15:

The investigator in his or her research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a subject, as well as a plan for how to manage such a disclosure.

Recommendation 16:

When research results are disclosed to a subject, appropriate medical advice or referral should be provided.

Considerations of Potential Harms to Others

The federal regulations governing the protection of research subjects extend only to individuals who can be identified as the sources of the biological samples. The exclusive focus of the regulations on the individual research subject is arbitrary from an ethical standpoint, because persons other than the subject can benefit or be harmed as a consequence of the research.

Recommendation 17:

Research using stored human biological materials, even when not potentially harmful to individuals from whom the samples are taken, may be potentially harmful to groups associated with the individual. To the extent such potential harms can be anticipated, investigators should to the extent possible plan their research so as to minimize such harm and should consult, when appropriate, representatives of the relevant groups regarding study design. In addition, when research on unlinked samples that poses a significant risk of group harms is otherwise eligible for exemption from IRB review, the exemption should not be granted if IRB review might help the investigator to design the study in such a way as to avoid those harms.

Recommendation 18:

If it is anticipated that a specific research protocol poses a risk to a specific group, this risk should be disclosed during any required informed consent process.

Publication and Dissemination of Research Results

Publishing research results with identifiable information in scientific or medical journals and elsewhere may pose a risk to the privacy and confidentiality of research subjects. Public disclosure of such information through written descriptions or pedigrees may cause subjects to experience adverse psychosocial effects. In addition, without the informed consent of the individual, such disclosure infringes on the rights of the subject or patient. Because of the familial nature of information in pedigrees, their publication poses particularly difficult questions regarding consent. Investigators and journal editors should be aware that the ways in which research results are publicized or disseminated could affect the privacy of human subjects. NBAC believes that the source of funding, i.e., public or private, should not be an important consideration in determining the ethical acceptability of the research.

Recommendation 19:

Investigators' plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups.

Recommendation 20:

Journals should adopt the policy that the published results of research studies involving human subjects must specify whether the research was conducted in compliance with the requirements of the Common Rule. This policy should extend to all human subjects research, including studies that are privately funded or are otherwise exempt from these requirements.

Professional Education and Responsibilities

Public and professional education plays an essential role in developing and implementing effective public policy regarding use of human biological materials for research. By education, NBAC is referring not simply to the provision of information with the aim of adding to the net store of knowledge by any one person or group; rather, education refers to the ongoing effort to inform, challenge, and engage. Widespread and continuing deliberation on the subject of this report must occur to inform and educate the public about developments in the field of genetics and other areas in the biomedical sciences, especially when they affect important cultural practices, values, and beliefs.

Recommendation 21:

The National Institutes of Health, professional societies, and health care organizations should continue and expand their efforts to train investigators about the ethical issues and regulations regarding research on human biological materials and to develop exemplary practices for resolving such issues.

Recommendation 22:

Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (government, private sector enterprises, and academic institutions) should work together to make these resources available.

Use of Medical Records in Research on Human Biological Materials

In recent years, attention increasingly has been paid by policymakers to the need to protect the health information of the individual. Extensive efforts at the state and federal levels to enact such protections have resulted in the setting of a variety of limitations on access to patient medical records. NBAC notes that debates about medical privacy are relevant to researchers using human biological materials in two ways. First, these researchers often need access to patient medical records, either to identify research sample sources or to gather accompanying clinical information. Such activities constitute human subjects research and should be treated accordingly. Second, the development of statutes and regulations to protect patient medical records could have the unintended consequence of creating a dual system of protections, one for the medical record and one for human biological materials. Moreover, restrictions on access to the medical record could impede legitimate and appropriate access on the part of investigators whose protocols have undergone proper review.

Recommendation 23:

Because many of the same issues arise in the context of research on both medical records and human biological materials, when drafting medical records privacy laws, state and federal legislators should seek to harmonize rules governing both types of research. Such

legislation, while seeking to protect patient confidentiality and autonomy, should also ensure that appropriate access for legitimate research purposes is maintained.

Appendix 3 Sample Informed Consent

SAMPLE INFORMED CONSENT NASA/JSC CONSENT STATEMENT FOR Collection and Storage of Human Biological Materials for Research Purposes NASA/JSC Specimen Repository

PURPOSE:

A “repository” is a storage bank of medical information. You are invited to give tissue/specimens/medical information about yourself for future research purposes to the NASA/JSC Specimen Repository. This facility was developed to study space flight related conditions. The goals of this research are to [list purpose of the research].

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, you will be one of approximately [xxxx] subjects who will be participating in this research.

DURATION OF SUBJECT’S PARTICIPATION:

The specimens will be stored for indeterminate period. [If not known, indicate such.]

PROCEDURE FOR THE STUDY:

If you agree to be in the study, we will be collecting human biological specimens which include healthy tissues such as blood, nail clippings, urine, feces, and sweat, and hair. These materials will be collected in one of two ways:

1. As an additional sample obtained at the time of obtaining a sample for a separate research project.
2. As part of a general request for a sample of human biological materials not associated with a particular research project or as part of your normal medical treatment.

There will be no medicines to take and no treatments provided as part of this collection effort.

Your tissues or medical data will be used for future NASA research directly related to the NASA mission. Prior to the release of any samples from the repository, the research will be determined to be important and scientifically valid. If the specimens will be de-identified, “future, unspecified use” is acceptable. By the very nature of such research being conducted in the future, it is difficult to define what future research methodology will entail and it may not be possible to identify all of the ways in which the specimen will be used. You may be told the results of any screening done on specimens, if applicable. Your tissue specimen or medical data may be shared with other investigators for additional analysis without making your identity known.

Other uses of the stored specimens will not be permitted without your reconsent. The possible creation of an immortalized cell line based on the specimen, if applicable, would require your reconsent. Human genetic research, including DNA typing, will require your specific consent.

STORAGE

In most cases the samples collected will need to be identified so that they can be linked to your medical information; however, the samples will be stored as coded samples, the identity of which will be linked to other demographic information in password-protected databases.

The biological materials will be stored in security protected collections belonging to and managed by the NASA/JSC Repository. We will use security measures to protect your samples/information, including password protected computer files. Before any research involving the specimens is conducted, the Committee for the Protection of Human Subjects (CPHS) must review and approve the research proposal. The Committee includes scientists and non-scientists, including community representatives. The purpose of the CPHS is to ensure that the interests of

individuals participating in research studies are well protected. The information in the repository will be available only to authorized staff. If specimens are identifiable, only the repository personnel will have access to the identifiers. Access will be given to investigators who seek the materials for research purposes, through approval by a repository committee.

Depending on the research, the following options are permissible:

1. Permitting only unidentified or unlinked use of biological samples in research,
2. Permitting coded or identified use of biological samples for one particular study only, with no further contact permitted to ask for permission to do further studies,
3. Permitting coded or identified use of biological samples for one particular study only, with further contact permitted to ask for permission to do further studies,
4. Permitting coded or identified use of biological samples for any study relating to the condition for which the sample was originally collected, with no further contact allowed to seek permission for other types of studies,
5. Permitting coded or identified use of biological sample for any study related to the condition for which the sample was collected with further contact allowed to seek permission for other types of studies).

RISKS OF TAKING PART IN THIS EFFORT

The physical risks associated with participation in this effort are [list risks of sample acquisition, if any... Any materials that are collected will be collected by experienced technicians to reduce the chance of any physical harms.]

[If appropriate, include the following: The major risk of your participation is the possible risk of loss of confidentiality of private medical information. (If tests results will be shared, list the potential fiscal, psychological, and social risks of disclosure of test results.)]

(If genetics studies will be performed, include the risks of participating in genetic studies including the effects of the knowledge that one is the carrier of a disease gene that might affect their life course, employability or insurability, if results will be shared. If subjects want to be told, list the precautions that will be taken to minimize the potential harm of receiving bad news and to preserve the confidentiality of the results. Also include the risks stigmatization of a subject or group, discrimination in insurance or employment, generation of conflict within a family, harm to relatives, inappropriate commercialization of findings, or use of samples in projects objectionable to the subject, if applicable).

Since we do not yet know the exact questions that will be studied by scientists in the future, we cannot tell you what specific information they will be looking at or what that might mean to you.

BENEFITS OF TAKING PART IN THE EFFORT

This is a research effort and is not intended to provide any direct health benefit to you. The benefits of research using tissue or data include learning more about space flight related effects on the human. This information may be valuable in preventing or treating space flight related conditions in the future.

CONFIDENTIALITY

Every effort will be made to keep your personal information confidential. In order to protect the confidentiality [list procedures to protect confidentiality, as applicable]. For example:

1. We will ensure that your personal information file is kept separate from the file containing information learned from your biological material and that the connections between these two files are secured by coding all identifiers.
2. The files can only be accessed by a limited number of staff.
3. Files will be made secure by encryption (use of a secret code unknown to unauthorized personnel) and will be maintained and accessed only by authorized staff.

4. The Repository manager has been assigned to manage the storage bank and is the only person able to relate your medical information to your name or identity. Should the storage bank ever be closed in the future, all identifying information about you will be removed so that it will never be possible to trace the information back to you.
5. The medical information you contribute to the storage bank will not be released to any insurance company, potential employer, government agent or agency, family member, or friend without your permission.

Your personal information may be disclosed if required by law, to federal regulatory agencies such as the Food and Drug Administration. In addition, your original medical records may be reviewed by the Committee for Protection of Human Subjects or its designees, or regulatory agencies. If the results from any research study of your tissue/medical information are ever published for scientific purposes, your name and identity will remain confidential and will not be mentioned in any reports.

The Repository Manager will release medical information for research purposes to answer specific research questions, but only when the study investigator has received approval from the Committee for Protection of Human Subjects responsible for overseeing this repository.

ALTERNATIVES TO TAKING PART IN THE EFFORT:

The alternative to participation in this research is to not give tissue or data to the repository. This will not alter your employment, care, or your relationship to any of your physicians. If samples are identifiable, you may also withdraw your tissue or data at any time by contacting the NASA/JSC Repository at ----(telephone number) No further use will be made of the samples/information you gave.

COSTS/COMPENSATION:

There is no financial cost to you for participating. There is no compensation provided for participation. Donating biological materials is an act purely to aid future medical and scientific research. In the event of physical injury resulting from your participation, necessary medical treatment will be provided to you. You are not giving up any legal rights or benefits to which you are otherwise entitled (Insert standard CPHS verbiage here).

RECONTACT FOR FUTURE USE [Use this section only if samples are identifiable]

In the future, investigators may design a particular research study that requires use of the biological material you have given as well as additional samples and/or information. If, in the future, we would like to obtain additional samples or information, we will need to contact you to request your permission. **Please indicate below whether or not you give permission for us to contact you about obtaining more information.**

I give my permission for researchers to contact me about obtaining additional samples and/or information.

I do not give permission for researchers to contact me about obtaining additional samples and/or information.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about this collection effort or a research-related injury, contact the researcher managing the collection of samples, at [telephone number].

For questions about your rights as a research participant or complaints about a research study, contact the CPHS at....

Due to unforeseen circumstances such as flood, fire, earthquake, tornado or electrical failure, your human biological materials may need to be discarded.

VOLUNTARY NATURE OF PARTICIPATION AND WITHDRAWAL

Taking part in this effort is voluntary. You may choose not to take part. Also, you may agree to have your material stored and later decide that you want to withdraw it from storage. If so, you should contact the investigator listed above and tell him or her to discard your sample or remove all personal identifiers. He, or she, will then discard your sample or remove the identifiers, but any data that has been obtained from testing your biological material that has been deidentified until that point will remain part of the research.

You can obtain access to your stored samples or data obtained from the samples for information that may be of clinical relevance to you.

COMMERCIAL USE OF HUMAN BIOLOGICAL MATERIALS

Although this is a research institution, specimens used for research purposes may not be used in an attempt to develop products to be sold.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent to participate in this collection effort. I acknowledge receipt of a copy of this informed consent statement.

SUBJECTS SIGNATURE:
(must be signed and dated by the subject)

Date:

SIGNATURE OF WITNESS:
(person obtaining consent.)

Date:

ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CDE	common data elements
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CPHS	Committee for the Protection of Human Subjects
FDA	U.S. Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act of 1996 [45CFR part 160 and subparts A and E of part 164]
IATA	International Air Transport Association
IRB	Institutional review board
ISBER	International Society for Biological and Environmental Repositories
NBAC	National Bioethics Advisory Commission
NBN	National Biospecimen Network
NBSR	NASA Biological Specimen Repository
NCI	National Cancer Institute
OBRR	Office of Biorepositories and Biospecimen Research (at the NCI)
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality assurance
QC	Quality control

GLOSSARY

Adverse outcome: An undesirable effect or untoward complication consequent to or reasonably related to specimen integrity (ISBER 2005).

Aliquot: A portion of a specimen that has been divided into separate, smaller parts, usually liquid, which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample (ISBER 2005).

Annotation: Explanatory or extra information associated with a particular specimen. Annotations may be added by the resource collector.

Anonymized Samples (Unlinked): Unlinked samples are those that may have been acquired from identified human sources, but all identifiers or codes have been removed and destroyed such that the ability to identify particular individuals, via clinical or demographic information, would be extremely difficult for the investigator, the repository or a third party.

Authorization: Express written permission that an individual permits the release and use of their individually identifiable health information for a particular purpose. Authorizations are not required to use an individual's health information to treat them, obtain payment or for a provider's health care operations. However, under HIPAA, research is not considered health care operations, and therefore requires an authorization or waiver of authorization with limited exception. The provider (or investigator) is responsible for obtaining an authorization from an individual.

Certificates of Confidentiality: In situations where the investigator requires protection of research of a sensitive nature, the principal investigator can apply to the Department of Health and Human Services to protect this information. This allows a researcher to protect the privacy of research subjects by withholding from all persons not connected with the research team the names and other identifying information relating to research subjects. The protection will be granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives. Examples include research relating to sexual attitudes, preferences, or practices, the use of alcohol, drugs, or other addictive products, pertaining to illegal conduct or to an individual's psychological well being or mental health, genetic information, information that,

if released, could be damaging to an individual's financial standing, employability, or reputation, and information that would normally be recorded in a patient's medical record that, if released, could lead to social stigmatization or discrimination. Researchers may receive a Certificate of Confidentiality regardless of funding source. Researchers who receive a certificate may not be compelled by Federal, State, or local legal processes or subpoenas to disclose information that they possess as a consequence of the research.

Clinical data: Data pertaining to or founded on actual observation and treatment of patients.

Clinical trial research: Research studies that evaluate new interventions, drugs, or medical therapies given to patients in strictly scientifically controlled settings. The purpose of such trials is to determine whether one or more screening, prevention, and/or treatment options are safe, effective, and better than current standard care.

Code of Federal Regulations (CFR): The Code of Federal Regulations is a publication that codifies the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the Federal Government. It is published by the Office of the Federal Register, National Archives and Records Administration, Washington, DC.

Coded samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number. The repository retains information linking the code to a particular human specimen. Information is sufficient such that the investigator, repository or third party could link the biological sample or information derived from the research using the sample with a particular person or small group of identifiable individuals.

Collector-Investigators: Persons charged with the responsibility of obtaining specimens from subjects for the purposes of adding to a repository.

Committee for Protection of Human Subjects (CPHS): A specially constituted review body established or designated to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.

Common Data Elements (CDEs): CDEs standardize metadata between a series of software systems. Such standardization ensures that the same meaning of words is used and that data model and application components are reusable. In addition, it eases the integration of systems.

Common Rule: Federal Policy for the Protection of Human Subjects codified at 45 CFR Part 46.

Custodianship: Relates to the caretaking responsibility for the specimen collection, including management and documentation, as well as rights to determine the conditions under which the specimens are accessed and used.

Data Sharing Policy: Sharing of final research data to serve these and other important scientific goals and the timely release and sharing of final research data for use by other researchers. 'Timely release and sharing' is defined as no later than the acceptance for publication of the main findings from the final data set.

De-identified protected health information: Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. Such information is not individually identifiable health information (45 C.F.R. §164.514(a)-(c)) (Eiseman). The Privacy rule requires one of the two following approaches to de-identify data:

- If a person with appropriate knowledge and experience applying generally accepted statistical and scientific principles and methods for rendering information not individually identifiable makes a determination that the risk is very small that the information could be used, either by itself or in combination with other available information, by anticipated recipients to identify a subject of the information.

OR

- If all 18 identifiers have been removed, including name, all geographic subdivisions smaller than a State including street address, city, county, precinct, zip codes and equivalent geocodes, (except for the initial 3 digits of a zip code if more than 20,000 people reside in the area), all dates including birthdays (other than the year) and ages over 89, phone numbers, fax numbers, email addresses, social security numbers, medical record numbers, health plan

beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers and serial numbers (including license plate #), device identifiers and serial #'s, URLs, IP addresses, biometric identifiers, full face photographic images and any comparable images, any other unique identifier, characteristic or code. Note: Other demographic information, such as gender, race, ethnicity, and marital status are not included in the list of identifiers that must be removed.

Demographic data: Data relating to statistical characteristics of human populations (e.g., age, gender).

Distribution: A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another repository, specimen collection center, or laboratory (ISBER 2005).

Genomics: The study of genes and their function; the study of all or a substantial portion of the genes of an organism as a dynamic system, over time, to determine how those genes interact and influence biological pathways, networks, and physiology.

Honest Broker: A neutral intermediary between the individual whose tissue and data are being studied and the researcher. The honest broker collects and collates pertinent information regarding the tissue source, replaces identifiers with a code, and releases only coded information to the researcher (Eiseman).

Identified specimens: Specimens which are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e., his or her relationship to a family member whose identity is known).

Identifiers: Identifiers are information that can be used to link a sample or scientific result with a specific person or group of people. Examples of identifiers include name, social security number, hospital number or other unique identifier. It should also be noted that using current information technology, a combination of descriptive data may be sufficient to allow identification of the donor and thereby collectively may be considered identifiers (e.g. zip code, birth date or profession may be sufficient to identify a specific individual).

Informatics: The use of science, computer science, information technologies, and other technologies to provide data, information, and knowledge to an individual or an organization. The term is synonymous with information science.

Informed consent: An educational process between the investigator and the prospective subject (or the subject's legally authorized representative) as a means to ensure respect for persons, mutual understanding of research procedures, risks, rights, and responsibilities; and continuous voluntary participation (NBN Blueprint 2003).

Institutional review board (IRB): A specially constituted review body established to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. (see CPHS).

Longitudinal data: Clinical data acquired over the course of time.

Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45CFR46.102). Studies involving treatments or procedures that are more invasive than a routine blood draw generally have more than minimal risks. Risk are also greater than minimal when identifiable information, if revealed outside the study, could be a risk to a subject's employment, insurance, financial standing or reputation or put a subject at legal risk.

Preservation: Use of chemical agents, alterations in environmental conditions, or other means during processing to prevent or retard biological or physical deterioration of a specimen (ISBER 2005).

Privacy: The state or condition of limited access to an individual and/or to information about that individual. Privacy protects access to the person, whereas confidentiality protects access to data.

Privacy Rule: A component of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Processing: Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling (ISBER 2005).

Prospective Study: A study in which the collection of tissue or other data related to the individual from whom the biological specimen was collected will occur "in the future". In other words the biological specimen is not "on the shelf" when approval for the research under review is requested. This may refer to tissue that will be obtained specifically for research purposes after the research protocol has been approved by the CPHS wherein the subject is asked to undergo a procedure to obtain a specimen for research purposes or specimens to be collected from discarded clinical samples for research purposes that will be obtained after the research is approved by the CPHS. By contrast, "retrospective" studies focus on information or samples already collected.

Protected Health Information (PHI): Any health information that is collected by a covered entity and is individually identifiable (NBN Blueprint 2003). Also, a subset of individually identifiable information that can be disclosed only under the following conditions: (1) the use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes, (2) no PHI is removed from the covered entity during review, and (3) the PHI that the researcher seeks to use or access is necessary for the research purposes. PHI can be de-identified by removing all 18 identifiers listed in Section 164.514(b)(2) of the Federal regulations or by having a qualified statistician perform an analysis stating that the risk of the information being used is small (ISBER 2005).

Quality Assurance (QA): An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project (ISBER 2005).

Quality Control (QC): Specific tests defined by the QA Program to be performed to monitor procurement, processing, preservation and storage, specimen quality, and test accuracy. These may include but are not limited to performance evaluations, testing, and controls used to determine accuracy and reliability of the repository's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment, and facilities (ISBER 2005).

Recipient-Investigators: Persons approved to receive specimens from a repository to use for research purposes.

Repository: a common site for storage of collections of human biologic specimens available for study. This may be one geographic location or may be a virtual aggregation of biologic specimens from many locations. Repositories are also referred to as tissue banks, collections, resources, inventories, or by other terms.

Retrieval: The removal, acquisition, recovery, harvesting, or collection of specimens (ISBER 2005).

Retrospective Study: Studies that utilize existing biological samples that have already been collected when the CPHS request for approval is made or for which there is no plan to recontact donors in order to obtain additional new information/data. This may refer to biological samples collected for clinical indications and then stored (i.e. pathology specimens, left over sera, etc.) or a secondary use of biological samples collected previously for another research protocol (i.e. "leftover" sera from a research study or material in a tissue bank).

Sample: Portions of specimens distributed to researchers (Eiseman).

Specimen: A portion of tissue, blood, urine, or other material used for diagnosis and analysis. A single biopsy may generate several specimens, including a number of slides, paraffin blocks, and/or frozen specimens. It refers to the quantity of material stored in the repository, whereas the term sample refers to an aliquot of the specimen supplied to investigators.

Storage: Maintenance of specimens for future use.

Tissue: Refers generally to a biologic collection of cells, Tissue is most often referred to in the context of solid tissue, as originating from a solid organ; however, tissue can also be defined broadly to include collections of cells and intercellular substances from bodily fluids such as blood.

Unidentified Specimens: Also known as “anonymized” For these specimens, identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the biorepository.

REFERENCES

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- HHS Human Subjects Regulations: 45 CFR part 46. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
- HIPAA Privacy and Research Guidance: <http://privacyruleandresearch.nih.gov/>
- HIPAA Privacy Rule “Standards for Privacy of Individually Identifiable Health Information, Final Rule”, August 14, 2002 at <http://www.hhs.gov/ocr/hipaa/privrulepd.pdf>
- Privacy Act of 1974, 5 U.S.C. § 552a http://www.usdoj.gov/oip/04_7_1.html

OHRP Policies

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- OHRP Human Subject Regulations Decision Charts 9/24/2004 <http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm>
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- OHRP Secretary’s Advisory Committee on Human Research Protections (SACHRP) Appendix E, February 9, 2005 at <http://www.hhs.gov/ohrp/sachrp/appendixe.html>
- Office for the Protection of Research Subjects Guidance for Researchers: Human Specimens Guidance http://www.usc.edu/admin/provost/oprs/private/docs/hsirb/forms/Repositories_Points_to_Consider.pdf

NASA Documents

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- NIH Office of Extramural Research Certificates of Confidentiality <http://grants.nih.gov/grants/policy/coc/background.htm>
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- NCAB (National Cancer Advisory Board). First-Generation Guidelines for NCI-Supported Biorepositories. 2005. http://biospecimens.cancer.gov/biorepositories/guidelines_full_formatted.asp

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- ISBER (International Society for Biological and Environmental Repositories). Best practices for repositories I: collection, storage and retrieval of human biological materials for research. Cell Preserv Technol 2005. 3:5-48.
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