Guidelines for Human Biospecimen Storage and Tracking within the NIH Intramural Research Program

Biospecimen Working Group

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Preface

Biological specimens (or "biospecimens") from study participants must be handled according to the highest ethical and scientific standards to maintain the public's trust, to preserve and protect the specimens and the substantial investment these resources represent, and to facilitate research by maximizing use of the specimens. These guidelines set forth essential principles and practices for handling, storing, and tracking human biospecimens within the intramural research programs (IRP) of the National Institutes of Health (NIH).

These guidelines complement the *Guidelines for the Conduct of Research in the Intramural Research Program at NIH* (1*), Standards for Clinical Research Within the NIH Intramural Research Program* (2), *Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH* (3), and existing NIH regulations for the conduct of research such as those governing human subjects research, animal use, radiation, chemical and other safety issues, transgenic animals, and the Standards of Conduct that apply to all federal employees.

These guidelines were originally developed by a committee appointed by the NIH Scientific Directors in 2007 and have now been revised to ensure that the most current guidance and resources are provided. In November 2012 the Scientific Directors reviewed and approved the revisions. The Working Group on Biospecimens made significant contributions to implementation of the new Biospecimen Reporting in the NIH DB as well as editing and revising the Guidelines. Additionally, this Group was recognized for their outstanding achievements by Dr. Collins with a Directors Award December 19, 2012.

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Introduction

All biospecimens collected by scientists in the NIH Intramural Research Program should be handled and stored following the best practices available. To ensure proper stewardship of human biospecimens within the NIH intramural research programs, the Deputy Director for Intramural Research and the Scientific Directors of the NIH have endorsed guidelines for biospecimen storage and tracking in relation to these topics:

1. **Legal and ethical considerations**
2. **Collection and storage**
3. **Inventory database systems and tracking**
4. **Quality management practices including standard operating procedures**
5. **Shipping and sharing**
6. **Custodianship**
7. **Frequently Asked Questions (FAQs)**
8. **Abbreviations**
9. **List of Biospecimens 2012**
10. **References**

Definition of Human Biospecimens

These guidelines apply to all human biospecimens that include blood and other body fluids, tissues, nucleic acids, and other direct derivatives from human tissues (4). Subsets of human materials and derivatives of the biospecimens, such as extracted DNA, or derived cell lines that are traceable to a human subject, i.e., collected on an IRB protocol, or with linked Personally Identifiable Information (PII), are also considered independent biospecimens.

While all biospecimens should be handled according to best practices, these guidelines apply specifically to specimens that are classified as:

- *"Identified,"* meaning that they or their associated data are attached to a readily available subject identifier (*e.g.,* social security number, address, telephone number, medical record number, *etc.*). These are most often collected through IRB approved protocols.

- *"Coded,"* meaning that they or their associated data are identified by use of a random or arbitrary alphanumeric code, but the biospecimens may still be linked to their sources through use of a key to the code available to an investigator or collaborator. An example of specimens of this type are materials provide by the NIH Department of Transfusion Medicine, where additional materials can be requested, but have no PII directly available to the Investigator.

- *"Unlinked,"* meaning that the original identifiers have been irreversibly stripped making it impossible for anyone to link the biospecimens to the sources. Biospecimens provided through collaborations may fall into this category, where they were originally collected with PII, which has been stripped.

- *"Unidentified,"* meaning that the biospecimens or data were collected without identifiers of any kind. Surgical tissues, cadaveric tissues, foreskins, and swabs which were all discarded materials would be considered as unidentified.

The terms "biospecimens", "specimens" and "samples" can be used interchangeably. The guidelines apply regardless of whether the biospecimens were originally collected for patient care-related purposes or for research and also apply regardless whether or not the individual from whom the specimen was originally collected is still living.

The guidelines do not apply to tracking and reporting of biological materials and derivatives that were obtained from commercial sources and are used as "reagents". For example,

reagents would include human cell lines or tissues purchased from ATCC or other vendors. In addition, human biospecimens or their derivatives that are put into animals or biological inventions that have been derived from human biospecimens are not covered by these guidelines.

1. Legal and ethical considerations

Human biospecimens used by NIH researchers must be collected, stored, used, shared, and disposed of in accordance with the informed consent signed by the subject, or under a waiver of informed consent granted by an independent ethical review body, in accordance with 45 CFR 46 - Protection of Human Subjects (5), as appropriate. Prospective and continuing NIH Institutional Review and approval is required for research using human biospecimens. Research may be exempt from the requirement for continuing IRB review and approval if the research involves unlinked or unidentified biospecimens. The NIH Office for Human Subjects Research Protection (OHSRP) is authorized to determine whether research activity using human biospecimens is exempt (6) and approval or a request for exemption must be submitted to OHSRP by the IRP investigator by completing the appropriate "Request for Determination" form on the OHSRP website (7).

2. Collection and storage

NIH researchers must safeguard individual privacy and handle PII in accordance with the Privacy Act of 1974 (8), as applicable and appropriate.

Human biospecimens should be collected using procedures appropriate for the type of biospecimen being collected and its intended uses, and they must be handled in accordance with the U.S. Occupational Safety and Health Administration's Bloodborne Pathogens Standard (9). Each laboratory or repository must have a Standard Operating Procedure (SOP) for labeling, handling, and storage of biospecimens. Biospecimens containing select agents or toxins are regulated under 42 CFR 73 (10). Please contact your Division of Occupational Health and Safety Biosafety specialist for further guidance on biospecimens classified as select agents or toxins.

Human biospecimens in storage must have a unique identifier, should be labeled with a printed label and should contain either a one-dimensional (1D) or two-dimensional (2D) barcode. If the biospecimen is associated with PII, the identifier must enable the investigator to link to a basic set of information on biospecimen acquisition or the protocol and informed consent under which the specimen was collected, as well as an NIH Clinical Center central biomedical and translational research information system patient identification number, as appropriate. The label should be able to withstand all potential transportation and storage conditions.

Biospecimens with no PII, (unlinked or unidentified materials) should be labeled in accordance with a SOP which must be developed in the custodian's laboratory, or by the repository. Minimum information should identify biospecimen type and date of acquisition.

All repositories, whether large or represented by individual freezers in laboratories, should follow best practices for specimen storage and retrieval (11, 12). Repositories should be operated using effective facility environments that include ambient temperature controls, good air circulation, lighting, and security. Systems should be in place to allow for local and remote temperature monitoring of freezers, refrigerators, and other temperature controlled environments. Repositories should have emergency preparedness plans that cover equipment failures and power interruption that include back-up storage capacity and back-up power supplies such as generators.

3. Inventory database systems and tracking

Human biospeicmens stored at NIH should be tracked using a computer-based inventory system that records the location and detailed information of every specimen in the repository (11).

Ideally, inventory systems should have the capacity to assign a unique identifier to each specimen, custodianship, link and track aliquots or derivatives, and track significant events such as thaws, receipt and or processing events, warnings, destruction, or transfers out of the repository. Systems should be able to generate reports on each of these conditions and activities and should be able to link to detailed information on clinical and other variables (*e.g.,* participant information, protocol number, informed consent, clinical and epidemiological data) to facilitate research and serve as an archive so that the information remains available for future use. Inventory systems must meet federal requirements related to data privacy and security, such as those in the Privacy Act (8) and those issued by the National Institute for Standards and Technology (13), where applicable.

The inventory system should have the capacity to provide data for an annual NIH-wide assessment of storage and tracking practices, as required by the NIH Reform Act of 2006. Investigators who indicate in their annual 'Z' report that they work with human biospecimens must report the numbers of human biospecimens, by type of specimens currently stored, along with information about labels and tracking systems used in the Biospecimen Report, which is now separate from the Annual Report. Information in the Biospecimen Report will be used to populate biospecimen types required for the NIH Database.

The tracking of historical collections of specimens obtained before guidelines were issued in 2008 should be upgraded to meet these revised guidelines when feasible with some exceptions. Tracking as a single entity should *only* be considered when entry and initiation of tracking of individual specimens within a historical collection is not feasible.

4. Quality management practices including standard operating procedures

All human biospecimen collections and repositories, whether large or represented by individual freezers in laboratories, should have written SOPs detailing the policies and procedures used to collect, process, handle, store, track, ship, and share biospecimens. Human biospecimens must be handled safely in accordance with OSHA regulations and recommendations, as applicable. The quality assurance program should include periodic evaluation of adherence to the standard operating procedures.

Repositories should perform an annual verification of the physical location of a random sampling of the biospecimens to confirm that the appropriate biospecimens are in the correct location, as indicated by the inventory system.

5. Shipping and sharing

NIH investigators must abide by the highest scientific and ethical standards to preserve the public's trust and the substantial investment these resources represent when planning for the distribution of specimens to others (14).

NIH researchers must utilize written agreements to document shipping and sharing of human biospecimens. Various types of agreements are used for the transfer of human biospecimens and investigators should consult with their IC's Technology Transfer Office regarding such transfers (15). Written agreements for the transfer of biospecimens to commercial laboratories for diagnostic or other routine analysis take different forms and may depend on whether the entity is a for-profit or private organization (*e.g.,* material transfer agreements, purchase orders, contracts).

Packaging and shipping of human biospecimens must conform to all applicable regulations and standards, including the U.S. Department of Transportation and International Air Transport Association standards (16). All personnel involved in shipping biological materials should be trained properly for both air and ground shipments (10). In addition, NIH researchers should use best practices to protect biospecimens from factors that could influence specimen integrity (*i.e.,* temperature, humidity, light, structural quality, and spill

containment) and to provide protection to workers, individuals involved in the transportation of the specimens, and the environment.

6. Custodianship

Human biospecimens obtained by NIH researchers are considered federal property and must remain in the custody of NIH unless transferred via a specific written agreement such as an MTA or CRADA to an outside organization. The investigator, as custodian, is responsible for ensuring that specimens are collected, processed, and stored properly, and used according to what is allowed by informed consent documents. The investigator as custodian is responsible for the effective transfer of the biospecimens, associated data (as appropriate), and consent documents to a new custodian should the investigator leave NIH or if a change needs to occur for other reasons.

Institutes should have procedures to evaluate at least biennially when and how to discard human biospecimens or make them available for sharing with other researchers if consistent with the informed consent, or through a waiver from an IRB, or an exemption from the NIH Office of Human Subjects Research in the Intramural Research Program at NIH (6). Investigators should follow the principles governing sharing of resources described in the guidelines for the Conduct of Research in the Intramural Research program at NIH (1).

7. Frequently Asked Questions (FAQs) for Trans-NIH Biospecimen Reporting, 2012

1. **Q**: Some scientists use the terms human "samples" and "biospecimens" interchangeably. What is the correct nomenclature?

A: For the purposes of NIH reporting, the terms are interchangeable. According to the *Guidelines for Human Biospecimen Storage and tracking within the NIH Intramural Research Program* (NIH Guidelines), an "original sample" is a biospecimen. All daughter vials, aliquots, slides, extractions, etc., are still biospecimens and every one should be counted.

2. **Q**: Will I be required to report my holdings of biospecimens twice, once for this new Biospecimen Report and again, for the Annual Report (NIDB)?

A: Yes and No. The Biospecimen Report has been separated from the investigator's Annual Report for purposes of the NIH-wide assessment of storage and tracking practices, mandated by Congress in the NIH Reform Act of 2006. This requires information on just the total number of biospecimens held by the NIH IRP, how they

are tracked, and how they are stored. You will need to specify the type of material for the annual report, but quantitative information will automatically be populated from the biospecimen report.

3. **Q**: I have four different types of material (DNA, RNA, PBMC, serum) from one parent biospecimen (whole blood). The parent sample is used up/discarded, so, how do I count these derivatives?

A: These new biospecimens represent four different material types, each of which should be counted. In addition, any aliquots made from one of the material types should also be counted separately.

4. **Q**: I have 10 aliquots of plasma which I am storing from the same original biospecimen. How should I count these?

A: These are 10 unique biospecimens and should be counted as a total of 10; or 11 if the parental biospecimen has a volume remaining.

5. **Q**: I have several 250mL bags of normal human plasma in freezer storage. At such a high volume, I wonder if I count this as one biospecimen.

A: Yes, each bag is counted as one biospecimen, regardless of its volume.

6. **Q**: I gave biospecimens to a collaborator at the Johns Hopkins University this year. These originally were counted as my biospecimens last year. Do I count them again this year because they were originally collected as part of an IRP project?

A: No, these have left your custody and are not your biospecimens. Your inventory system should be updated to reflect that they were transferred out of the NIH.

7. **Q**: All of my research activities have received exemptions from the Office of Human Subjects Research Protections. Do I need to count the specimens that are a part of these studies?

A: Yes, these should be reported as human biospecimens for this report.

8. **Q**: Our lab has samples dating to the 1950s, prior to the establishment of IRBs. How do I enter these, if at all?

A: All biospecimens, regardless of age, labeling, or storage conditions, should be counted. When entry and tracking of individual specimens is not feasible, they may be counted as a single entity, with proper documentation. It is up to each project PI

to determine the best practices for culling and consolidating biospecimens of questionable quality and value, within the guidelines of their respective IRB.

9. **Q**: I received anonymized biospecimens as part of an MTA from my collaborator at University of Maryland. Do I count these as my biospecimens even though they were not collected under an intramural project originally?

A: Yes, because they will now be used as part of your research. Even if specimens have been irreversibly stripped of any identifiers or if the specimens were collected without identifiers, they need to be counted as part of your research collection.

10. **Q**: I purchased human HeLA and K562 cell lines from a company. Do I count these as biospeicmens?

A: No, since these are commercially available materials they need not be reported.

11. **Q**: SAIC-Frederick, Inc. repositories house many biospecimens for our laboratory and report the totals differently than we do. How should I deal with this?

A: It is the responsibility of each project's PI to report the biospecimens under their custody according to NIH Guidelines. Biospecimens stored in contractor-run repositories are still considered to be under the custodianship of the NIH PI and should be reported

12. **Q**: There are two PIs on my DIR project. Which one of us will count our biospecimens in our reporting?

A: Co-PIs must agree who will be the custodian of the biospecimens for reporting purposes so that the numbers are not duplicated in the totals. Then, one PI will count these in their reporting.

13. **Q**: I have an intramural collaboration in Cambodia and house biospecimens there in freezers. Should I count these in the totals?

A: Yes, these are human biospecimens collected for an intramural project, where an intramural PI has part custody, and as such, are federal property. They need to be reported unless the collection is officially transferred to another organization.

14. **Q**: DAIDS/NIAID funds numerous extramural network clinical trials, and biospecimens are being analyzed all over the world. Do we need to count these biospecimens?

A: Custodianship resides with the extramural investigator(s). However, if biospecimens return to NIH for any analyses, such as at the Vaccine Research Center (VRC/NIAID), they become part of the NIH collection and should be counted at that time.

15. **Q:** I will be receiving 10,000 biospecimens from our clinical trial immediately after I submit this biospecimen total report. How should I account for these biospecimens?

A: These totals will be captured during next year's reporting cycle.

16. Q: The NIH Dept. Transfusion Medicine (DTM) provides me with normal human lymphocytes from individual donors to use in my experiments. Do I count these as biospecimens?

A: Yes, the NIH DTM is storing and providing biospecimens for research, collected from human subjects under consent and IRB approval. They were transferred to you, and if they were not completely used in experiments and are still in storage by the report closing date (June 30), they must be counted.

17. **Q**: The human specimens I receive from DTM are used as controls. Do they need to be bar coded and accounted for in the survey?

A: Only those cells that remain in storage at the end of the reporting year must be counted.

18. **Q**: I isolated purified Plasmodium specific antibodies from a patient in 1986, and use these in my research assays. Are these considered biospecimens?

A: Yes, these antibodies were derived from a biospecimen obtained from a human subject. If you still maintain private identifiable information, the antibodies fall into the category of direct derivatives and should also be considered biospecimens.

The FAQs are also available on the NIH Sourcebook as a separate document and will be updated annually.

8. Abbreviations

CMV	Cytomegalovirus

CRADA	Cooperative Research and Development Agreement
CTA	Clinical Trial Agreement
DOT	Department of Transportation
EBV	Epstein-Barr Virus
IAA	Interagency Agreement
I.A.T.A.	International Air Transport Association
IRB	Institutional Review Board
iPSCs	Induced Pluripotent Stem Cells
MOU	Memorandum of Understanding
MTA	Material Transfer Agreement
NIDB	NIH Intramural Data Base
OHSRP	Office of Human Subjects Review Protection
OSHA	Occupational Safety and Health Administration
PBMC	Peripheral Blood Mononuclear Cells
PHI	Personal Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
RBC	Red Blood Cells
SLA	Simple Letter of Agreement
SOP	Standard Operating Procedure
WBC	White Blood Cells

9. Biospecimen List 2012

Blood or Blood Derivatives

Blood, Cells (buffy coat, WBC, PBMC, RBC, Clot)

Blood, Whole (Umbilical Cord, menstrual)

Blood, Serum/Plasma,

Body Fluid or Substance

Amniotic Fluid

Ascites or Peritoneal Cavity Fluid

Bile

Breast Milk

Bronchial or Pleural Fluids

Cerebrospinal Fluid (CSF)

Cerumen

Cervical Secretions

Colostrum

Eggs/Oocytes

Eye Fluids

Gallstones

Gastric Secretions

Kidney Stones

Nipple Aspirate

Pericardial Fluid

Prostatic Fluid

Rectal Secretions

Saliva/Buccal Cells

Sebum

Semen

Sputum

Stool

Swabs (any)

Sweat

Tears

Urine

Vaginal Secretions

Genomic

DNA

Protein

RNA

Human Cell Lines (derived at NIH or by collaborators)

EBV transformed

CMV transformed

iPSCs (with linked PII)

Tissue

Adipose

Adrenal Gland Specimen

Artery Tissue Specimen

Bile Duct Tissue Specimen

Bladder Tissue Specimen

Bone Marrow Specimen
Bone Specimen
Brain Tissue Specimen
Breast Tissue Specimen
Bronchial Tissue Specimen
Cartilage Specimen
Central Nervous System Tissue
Colon Tissue Specimen
Duodenal Tissue Specimen
Embryonic Tissue Specimen
Endocervical Specimen
Endometrium Specimen
Esophageal Tissue Specimen
Eye Tissue Specimen
Cataract Specimen
Fallopian Tube Specimen
Fetal Tissue Specimen
Gallbladder Tissue Specimen
Gastric Tissue Specimen
Hair Specimen
Heart Tissue Specimen
Pericardial Tissue Specimen
Histopathology Slides
Ileal Tissue Specimen
Jejunal Tissue Specimen
Kidney Tissue Specimen
Liver Tissue Specimen
Lung Tissue Specimen
Lymph Node Specimen
Middle Ear Tissue Specimen
Miscellaneous Tissue Specimens
Muscle Specimen
Nail Specimen
Nasopharynx Specimen
Nerve Specimen
Nose Specimen
Oral Cavity
Ovary Specimen
Pancreas Specimen
Paraffin Tissue Blocks
Parathyroid Gland Specimen
Peritoneal Tissue Specimen
Pharynx Specimen
Placenta Specimen
Pleura Specimen
Prostate Tissue Specimen
Rectal Tissue Specimen
Skin Specimen
Small Intestine Tissue Specimen
Soft Tissue Specimen
Specimen from Non-Specified Site
Specimen of Product of Conception
Stoma Specimen
Tendon Specimen
Testes Specimen
Thymus Specimen

Thyroid Gland Specimen

Tongue Specimen

Tonsil Specimen

Trachea Specimen

Ureter Tissue Specimen

Urethra Tissue Specimen

Uterine Cervix Specimen

Uterus Specimen

Vaginal Tissue Specimen

Vocal Cord Specimen

Vulva Specimen

Conclusion

Human biospecimens are a valuable resource and are essential to the biomedical research conducted at the NIH. They must be collected, stored, tracked, and used, according to the highest scientific and ethical standards. These guidelines provide a framework for NIH scientists for handling human biospecimens appropriately and maximizing their use in research.

10. References

1. Guidelines for the Conduct of Research in the Intramural Research Program at NIH, 4th edition, 2007 (http://sourcebook.od.nih.gov/ethic-conduct/Conduct%20Research%206-11-07.pdf)
2. Standards for Clinical Research Within the NIH Intramural Research Program at NIH (http://www.cc.nih.gov/ccc/clinicalresearch/index.html)
3. Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH (http://www.nihtraining.com/ohsrsite/New/COI-CR_1-4-2005FIN.pdf)
4. NIH requirements for the research use of stored human specimens and data (http://ohsr.od.nih.gov/info/sheet14.html)
5. 45 CFR 46 Protection of Human Subjects (http://ohsr.od.nih.gov/guidelines/45cfr46.html)
6. NIH Office for Human Subjects Research, (http://ohsr.od.nih.gov/info/DDIR.html).
7. OHSR Forms (http://ohsr.od.nih.gov/info/info.html)
8. The Privacy Act of 1974 (http://www.justice.gov/opcl/privstat.htm)
9. Occupational Safety and Health Administration's Bloodborne Pathogens Standard (7) http://osha.bloodbornepathogens.us/
10. 42 CFR 73, Select Agents and Toxins (http://www.selectagents.gov/select%20agents%20and%20Toxins%20list.html
11. ISBER Best Practices For Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research, 3rd edition (http://www.isber.org/bp/BestPractices2012.pdf)
12. NCI Best Practices for Biospecimen Resources, National Cancer Institute Office of Biorepositories and Biospecimen Research (http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf)
13. National Institute for Standards and Technology (http://csrc.nist.gov/index.html)

14. Policy for the Transfer of Materials from NIH Intramural Laboratories (http://www.ott.nih.gov/PDFs/Policy-for-the-Transfer-of-Materials.pdf)

15. Model agreements can be found on the web site for the Office of Technology Transfer at NIH (http://www.ott.nih.gov

16. International Air Transport Association standards (www.iata.org)