

THE JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH
COMMITTEE ON HUMAN RESEARCH

Research Involving Human Biological Materials

Policies, Guidelines, and Procedures
Revised April 2001

Definitions

Human Biological Materials

Human blood, fluids, tissues, cells, DNA, organs, or biopsy materials; aka “specimens”

Specimens

Human biological materials

Repository

A collection of human biological materials

Unidentified Specimens

Specimens in which personal, identifiable information has not been collected, maintained, or is retrievable by the repository.

Identified Specimens

Specimens to which is linked personal, identifiable information so that the donor may be identified.

Research Samples

Collections of human biological materials provided by repositories or collected by investigators in the course of research.

Unidentified Samples

Samples provided to investigators by repositories from unidentified specimens; aka “anonymous” samples

Unlinked Samples

Samples from which identifiers have been removed; aka “anonymized” samples

Coded Samples

Same as “linked” or “identifiable”. Samples provided by repositories from identified specimens. (The repository “codes” the samples in such a way that the investigator would not have any personal, identifiable information, but such coding or translation exists, and the samples are thus identifiable.)

Identified Samples

Samples provided by repositories from identified specimens with personal, identifying information.

Existing Materials

Materials that are “in the freezer” at the time the research is proposed.

Publicly Available Materials

Materials that already exist at the time the research is proposed, and are available to the general public. Materials that are obtained by qualified researchers for a nominal fee are not considered publicly available materials. “Publicly available” is defined by OHRP as unrestricted access on demand.

Research

A systematic investigation designed to develop or contribute to generalizable knowledge. (46 CFR 102 (d).

Minimal Risk

Risk is minimal when the probability and magnitude of harm or discomfort to a subject anticipated from the proposed research is not greater than what would be ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Introduction

Research on human biological materials poses additional challenges for researchers as new technology is developed in diagnosing and studying disease. A number of ethical issues have been raised regarding the appropriate use of human biological materials in research; these issues include the appropriateness of using a sample for research other than what was originally intended, physical and non-physical harm to individuals or groups, and privacy and confidentiality.

Policies, guidelines, and procedures governing the use of human biological materials must allow researchers the ability to pursue their scientific aims without compromising the rights and welfare of human subjects. In pursuit of appropriate guidelines to govern research on the human biological materials, the President's National Bioethics Advisory Commission (NBAC) issued final recommendations to then-President Clinton in August 1999, to provide guidance for IRBs and investigators. The guidelines outlined in this packet were developed from the NBAC's recommendations and the DHHS regulations on Human Research 45 CFR 46, also known as the Common Rule.

As new regulations evolve for research involving human biological materials, the Committee will revise these guidelines as required.

General Information

The Committee on Human Research reviews all proposed research involving human subjects, which includes research on human biological materials regardless of the funding source or the availability of funding. These regulations apply to all human biological samples, including blood, fluids, tissues, cells, DNA, organs, or biopsy materials.

Human biological materials can be categorized as either: (1) specimens maintained in a repository or (2) samples obtained from a repository. Specimens are collections maintained by repositories and may be either unidentifiable or identifiable. Unidentified specimens are specimens where there was either no personal identifying information collected, or where any such identifying information has been destroyed or is otherwise unavailable. Identifiable specimens are specimens that are linked to personal identifying information.

Materials obtained from a repository are known as research samples. Samples may be unidentified, unlinked, coded or identified. Unidentified samples are also known as "anonymous" samples. These samples are supplied to the investigator from unknown specimens. Unlinked samples are also referred to as samples that have been "anonymized". Unlinked samples do not have identifiers that can link the sample to an identified specimen. Coded samples, also known as "linked" or "identifiable," are samples that have codes that have been supplied by identified specimens. Identified samples are samples with personal identifying information obtained from identified specimens.

Federal regulations provide for three types of review for research involving human biological materials: (1) full IRB review, (2) expedited review, and (3) exempt review. In general, when using coded/identified samples, the Federal regulations require full IRB review. Minimal risk studies involving existing human biological materials may be eligible for expedited review regardless of how the materials were collected.

Guidelines for submitting a research project on human biological materials involving the types of samples to be used, as well as the Committee's policy on the appropriate review, are outlined in this packet. The guidelines are intended to be an addendum to the CHR's general protocol submission requirements.

Research on Human Biological Materials from Existing Collections

The OHRP interprets "existing" collections to mean any materials that already have been collected; that is, the materials are "in the freezer" at the time the research is initiated. The materials may have been collected specifically for research purposes or as part of clinical practice.

A. Research Using Coded or Identified Samples NOT in the Public Domain

Coded samples are samples that do not directly contain any identifying information (such as the subject's name or social security number). The repository codes the samples given to the investigator, and is able to link the sample to the source of the specimen. Because the potential to identify individuals using the "code" exists with coded samples, coded samples are considered identifiable. Identified samples are samples with personal identifiers that can directly link the sample with an individual.

Protocol applications for research on human biological materials using coded/identified samples not in the public domain must address the following in the research plan and informed consent document:

Research Plan

1. A thorough justification of the research design, including a description of the procedures used to minimize risk to subjects. Research using stored human biological materials poses potential harm to groups as well as to individuals. When appropriate, provide the plans for minimizing potential harm to an associated group. (It is recommended that if there may be potential harm to a particular group, they be consulted on the study design.)
2. A description of the process for obtaining the samples. If the samples will be obtained from a repository, a copy of the usage agreement from the repository or source must be submitted along with the protocol application. The investigator must supply the repository with a statement

verifying that the project will be conducted in compliance with applicable federal regulations (the CHR statement of approval may serve this purpose) or an explanation, in writing, of why the research is not subject to the regulations.

3. The type of samples to be used in the project (coded or identified).
4. The plans to obtain access to medical records, if any, or if contact will be made with the subjects.
5. A description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.
6. The plans for conveying research findings to the subject. If genetic studies will be conducted, the Research Plan must describe the steps to minimize potential physical, psychological, and fiscal risks to both the subject and the subject's family. In general, findings should not be conveyed unless they are confirmed and are clinically significant or scientifically relevant.

Informed Consent

All research using coded or identified samples not in the public domain requires the consent of the source unless the Committee grants a waiver or an alteration of the consent requirements. If a waiver or alteration of the informed consent requirements (45 CFR 46.116(d)) is requested, the request must include: (1) a justification that the research involves no more than minimal risk, (2) why the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) why the research could not be practicably carried out without the waiver or alteration, and (4) the plans for providing subjects with additional pertinent after the research is completed.

A copy of the consent document that was used to obtain the specimen must be included with the protocol application. The Committee will determine if the consent document meets the Federal requirements of informed consent. If the Committee determines that the previously obtained informed consent is inadequate and a waiver or alteration has not been granted, the original subjects who provided the specimens or samples must consent to the proposed research. A consent form to be submitted for review by the Committee must include the following:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed.
5. Identification of any procedures that are experimental.

6. A description of any reasonably foreseeable risks to the subject, and a description of any benefits to the subject or to others that may reasonably be expected from the research.
7. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
8. A statement describing the mechanisms to maximize protection against inadvertent release of confidential information.
9. A statement that there may be commercial profit from an immortalized cell line, if applicable.
10. For research involving more than minimal risk, an explanation as to whether any compensation is provided, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained.
11. If it is anticipated that the research project may pose a risk to a specific group, include a description of how this might affect the group.
12. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
13. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled.
14. The circumstances, if any, under which the sources will be re-contacted and a statement for the plans for access to medical records, if applicable.
15. The plans for conveying research findings to the subjects. If genetic studies will be conducted, include a statement on potential physical, psychological, and fiscal risks to both the subject and the subject's family.

B. Research Using Unidentified Samples, Unlinked Samples or Coded/Identified Samples that ARE Publicly Available

The Committee on Human Research reviews all research involving human biological materials eligible for exempt status under the Federal guidelines. Minimal risk studies conducted with unidentified samples, unlinked samples, and studies conducted with coded or identified samples that are publicly available may be eligible for exempt status.

In some cases, the Committee may not make the determination that a study is exempt even though the research meets the criteria for exempt status. For example, the Committee may determine that

the study is more than minimal risk if the potential for harm exists to a particular class of individuals with similar traits or characteristics (groups) or to participants in a small study with findings unique enough to allow easy identification of the individual.

Research on unlinked samples created from coded or identified samples in the investigator's possession may be eligible for exempt status if: (1) the Committee approves the process proposed for unlinking the samples, (2) the Committee determines that the scientific merit of the research will not be compromised by unlinking the samples, and (3) there may be no potential harm to an individual or to a particular group.

If a study is being submitted for consideration of exempt status, the investigator must submit a memo to the Committee indicating the following:

1. The name of the study.
2. The type of samples (unidentified, unlinked, or coded/identified samples that are publicly available). Studies that will use unlinked samples from coded or identified specimens in the investigator's possession, must include: (a) a description of the process for unlinking the samples, and (b) justification that unlinking the samples will not unnecessarily reduce the value of the research.
3. How the samples will be obtained.
4. If the samples will be obtained from a repository, include a copy of the consent document used to collect the samples, a copy of the repository's latest IRB approval, and a copy of the repository's usage agreement.
5. The source of the samples.
6. The sample size.

Collection and Storage of Human Biological Samples for Future Use

Protocol applications for research projects that will collect and store human biological materials for future use in the process of conducting research must address the following in the research plan and informed consent document.

Research Plan

The points outlined in this section are in addition to the 9 points outlined in the Application Form (CHR Form A).

1. A description of the process for obtaining the samples.
2. The type of samples to be collected and stored (human blood, fluids, tissues, cell line, DNA, organs or biopsy materials).
3. How the sample will be stored (unidentified, identified, unlinked, or coded).
4. The plans for re-contacting subjects, if any.
5. The length of time the samples will be stored. For example, transformed cell lines should not indicate limits. Stored DNA samples should indicate a defined arbitrary time (i.e., for the period of the study). Stored tissue samples should indicate a defined time period.
6. The plans for sharing the samples with other investigators, if any.

Informed Consent

If the samples will be collected during the process of conducting research, the consent for storage should be separate from the consent to research.

When samples are obtained in a clinical setting and informed consent for the research of biological materials is required, it should be obtained separately from the consent to clinical procedures.

1. A statement that the subject's sample will be collected and stored for research in the future.
2. The circumstances, if any, under which the sources will be re-contacted for future studies.
3. The length of time the sample will be stored.
4. A number of options to help the subject fully understand the decision they are about to make. For example:
 - a. Refusal to allow their sample for future use.
 - b. Permission to use only their unidentified or unlinked biological material in future research. An explanation must be included that by rendering the sample unidentifiable, access to research findings by either the donor or the donor's descendants will not be possible.
 - c. Permission to use their coded or identified biological material for a particular study, with no further contact permitted to ask for permission to do further studies.
 - d. Permission to use their coded or identified biological material for a particular study only, with further contact permitted to ask for permission to do further studies.

- e. Permission to use their coded or identified biological material 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.
 - f. Permission to use coded use of their biological materials for any kind of future study.
(Debatable Point: Some IRBs believe that a subject is not able to give informed consent for donating samples for future studies with unknown risks and benefits.)
5. A statement that there may be possible commercial profit from an immortalized cell line, if applicable.
 6. A statement that the subject may request that their donation for future use be withdrawn at any time by either requesting that the sample be destroyed or anonymized. If the subject requests that the donation be anonymized, a statement must be included that access to research findings that may affect the donor or the donor's descendants will not be possible.
 7. A statement on the subject's control over third party access to the stored samples.
 8. A statement that there may be commercial profit from an immortalized cell line, if applicable.

Criteria for Evaluating Previously Obtained Informed Consent for Research Using Identified or Coded Samples

1. What were the conditions under which the specimen was collected (e.g., clinical setting or as a part of a research protocol)?
2. Does the language or context of the consent form indicate that the source was interested in participating in the type of research being proposed?
3. If the source consented to the sample being used in unspecified future studies, is the consent document adequate for the type of research being proposed?
4. Did the source infer consent for research related to a particular disorder?
5. Should the investigators inform the source that research is being proposed with the sample or would re-contacting an individual source be inappropriate? (i.e., if explicit consent was never obtained due to a waiver, potential harm may arise should a subject learn that the specimen was used in an experiment.)
6. Should the subjects be given the opportunity to "opt out"?

7. If the IRB determines that the existing consent is inadequate, subjects should be contacted and informed consent must be obtained.

Application for Repository

The operation of human biological materials repositories and associated data management centers, regardless of funding source, is subject to review by the Committee on Human Research. The Federal regulations regarding human biological materials repositories apply to non-exempt research as defined under the Federal regulations. The CHR extends this policy to all research involving biological materials, both exempt and non-exempt research. Therefore, research involving human biological materials without identifiers or linkage to any personal identifying information may be certified by the Committee as exempt from the Federal regulations.

A human biological materials repository is a collection of specimens with or without accompanying data collected and stored during clinical procedures; specimens donated to blood, organ, tissue, or DNA banks; or specimens collected as part of a research project. Repositories collect, store, and distribute human biological materials for research purposes. Repository activities involve three components: 1) the collectors of materials, 2) the repository storage and data management center, and 3) the recipient investigators. Each component of the repository is governed by certain Federal regulations.

Any collection of human biological materials is considered to be a repository when there is no explicit plan to destroy the materials when the specific research project that generates the materials ends.

Oversight of a Repository

The OHRP and thus the CHR distinguish between the collection of human biological materials per se, their storage, and any modification or use subsequent to the original research project that generated the collection of materials. The following four scenarios represent the conditions for which specific additional CHR oversight is required. These four scenarios trigger the identification of the collection as a formal repository. In addition to seeking CHR approval for any research project utilizing the collection, the investigator must also seek separate approval for the operation of the repository (although the two requests for approval may be bundled into a single CHR application). The repository approval must explicitly address the 10 points outlined by the OHRP guidance issued (August 19, 1996) and summarized in this policy.

CHR oversight of repositories is required under the following conditions:

1. When the materials are collected as part of a research project and the investigator does not specify that after analysis the materials will be destroyed.

2. When the collector/investigator proposes to conduct a new analysis on samples from an existing collection in their possession. NOTE: The investigator must also submit a CHR application for the proposed research.
3. When collectors (SHSPH investigators and/or outside investigators) wish to add additional materials and/or data to an individual investigator's existing collection. NOTE: The CHR must review the informed consent document for the collection of the materials and/or data approved by the originating IRB.
4. When the materials stored in the collection will be shared with a recipient investigator.

A written usage agreement for recipient investigators should be developed, and should include the following:

“Recipient acknowledges that the conditions for use of this material are governed by the repository Institutional Review Board (IRB) in accordance with the Department of Health and Human Services regulations contained in 45 CFR 46. Recipient agrees to comply fully with all such conditions and to report promptly to the repository any proposed changes in the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to applicable State or local laws or regulations and institutional policies which provide additional protections for human subjects.

This research material may only be utilized in accordance with the conditions stipulated by the materials repository IRB. Any additional use of this material requires prior review and approval by the materials repository IRB and, where appropriate, by an IRB at the recipient site, which must be convened under an applicable OPRR-approved Assurance.”

NOTE: The CHR must review 1) the informed consent document for the collection of the materials and/or data approved by the originating IRB and 2) must be provided with a copy of the recipient site's IRB approval.

Informed Consent for the Collection of Materials to be Stored in the Repository

The informed consent document for the donation of materials may be included as part of the consent for the research project or submitted as a separate informed consent document. (The Committee suggests that a separate document address the storage of the materials.)

If the donation is included as part of the consent for the research, the subject must be given an option of whether or not they wish to donate their materials to the repository.

In addition to the basic elements of informed consent, the consent should include a clear description of the operation of the repository, including:

1. The specific types of research to be conducted. Identifiable materials may only be stored in a repository for research relating to the disease stated in the original protocol. Unidentifiable materials do not need to be limited to the disease stated in the original protocol but this option must be part of the consent.
2. The conditions under which data and specimens will be shared with other investigators. The CHR does not permit identifiable/coded materials to be shared with other investigators.
3. The procedures for protecting the privacy of subjects and maintaining confidentiality. The Committee recommends that a Certificate of Confidentiality (COC) be obtained for human cell repositories, specimens and data. The informed consent document should indicate that materials in the repository will be covered under the COC.
4. Where human genetic research is anticipated, the informed consent document should include information about the consequences of DNA typing.
5. Exculpatory language is not permitted through which subjects are made to waive or appear to waive any legal rights.