WHERE CAN YOU FIND HELP AND ADDITIONAL INFORMATION?

- Your institution's IRB
- The Office for Protection from Research Risks (OPRR)
- Your NIH institute/center Program Official
- The following web sites:

Office for Protection from Research Risks
http://ohrp.osophs.dhhs.gov/

NCI Resources Development Branch
http://cancerdiagnosis.nci.nih.gov/about/index.html#rdb

Bioethics Resources on the WEB
http://www.nih.gov/sigs/bioethics/

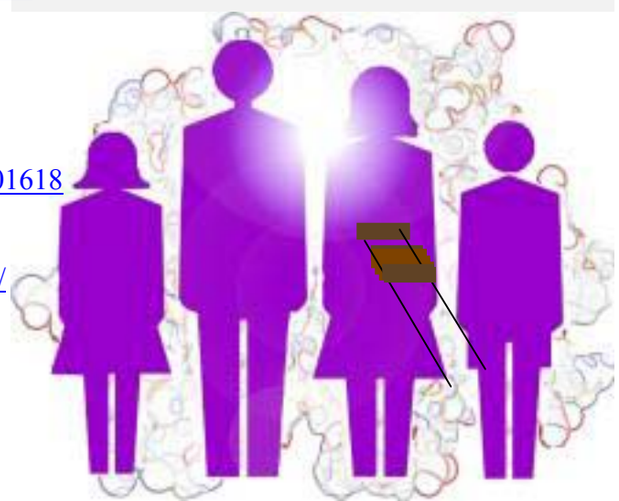
NHGRI Ethical Legal and Social Issues Program
http://www.genome.gov/page.cfm?pageID=10001618

National Bioethics Advisory Commission
http://www.georgetown.edu/research/nrcbl/nbac/

American Society for Investigative Pathology
http://asip.uthscsa.edu/pubaff.html

RESEARCH ON HUMAN SPECIMENS

ARE YOU CONDUCTING RESEARCH USING HUMAN SUBJECTS?



National Institutes of Health

ARE YOU CONDUCTING RESEARCH USING HUMAN SUBJECTS?

A 'human subject' is a living individual about whom an investigator obtains either (1) data through intervention or interaction with the individual, or (2) identifiable private information[1]. Legal requirements to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using human tissue specimens are often unsure about how regulations apply to their research. Legal obligations to protect human subjects apply, for example, to research that uses-

- **Bodily materials,** such as cells, blood or urine, tissues, organs, hair or nail clippings, even if you did not collect these materials
- **Residual diagnostic specimens**, including specimens obtained for routine patient care that would have been discarded if not used for research
- **Private information**, such as medical information, that can be readily identified with individuals, even if the information was not specifically collected for the study in question. Research on cell lines or DNA samples that can be associated with individuals falls into this category.

IF SO, YOU MUST...

Comply with your institution's rules and the requirements of your Institutional Review Board (IRB) as well as meeting Federal requirements[1] in order to carry out your research. Some institutions have requirements that exceed those of the Federal regulations. If you have any question or uncertainty about whether you need IRB approval, you should ask your IRB office for clarification[2]. If you apply for an NIH grant or respond to a Request for Contract (RFC), failure to follow your institution's procedures or to document the use of human tissues or data in your grant application or contract proposal can create problems and may delay funding or preclude award.

1. Title 45 Code of Federal Regulations, Part 46 (June 18, 1991).
2. If your institution has no IRB you may establish an IRB at your own institution and obtain Federal approval for the newly-created IRB, or you may obtain approval for your use of human subjects from an IRBelsewhere that satisfies all Federal requirements. For more information about these options contact the Office of Protection from Research Risks.
3. Title 45 Code of Federal Regulations, Part 46.116.

WHAT IS THE ROLE OF MY INSTITUTIONAL REVIEW BOARD?

The IRB at your institution must review and approve research if it involves human subjects. This process is designed to ensure that the research protects the rights and welfare of human subjects-for example, by minimizing risks, selecting subjects equitably, obtaining informed consent and ensuring privacy and confidentiality.

IRB approval must precede initiation of any work involving human subjects. No NIH grant or contract can be awarded until IRB approval is obtained. If the research continues, the IRB must review and approve the project at least once a year. When changes occur in the procedures with human subjects, the IRB must review and approve these changes.

If human subjects are harmed, including physical injury, improper disclosure of private information, economic loss or other harmful occurrences, the IRB must be notified.

TYPES OF IRB REVIEW

Full Board Review -Review of proposed research at a convened meeting at which a valid quorum of IRB members is present. For the research to be approved, it must receive the approval of a majority of those members present.

Expedited Review -Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

WHAT CONSENT IS REQUIRED FOR THE USE OF HUMAN TISSUE SPECIMENS?

IRBs are responsible for determining whether or not informed consent is required from the subjects from whom the specimens were obtained. The IRB may waive the requirement for informed consent if the risk to the subjects is minimal and if certain other conditions are met.[3]

You should not assume that your research poses minimal risk just because it involves tissue specimens. Loss of confidentiality can cause harm to patients and their relatives; IRBs will consider whether privacy and confidentiality protections are adequate.

IS MY RESEARCH EXEMPT FROM IRB REVIEW?

Research with specimens and data from living persons is exempt from the requirement for IRB approval when it is determined that the research either does not involve human subjects as defined in the Code of Federal Regulations (CFR) or the only involvement of human subjects is in one of the "exempt" categories listed in the Code. The exemption that is most pertinent to work with human tissue specimens is exemption #4.

As stated in 45 CFR 46.101(b):

"Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:
...(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects."

Some researchers mistakenly believe that any studies on existing pathology specimens are exempt. Exemption #4 does not apply to specimens that are linked to patient identity, even if the subject identifiers are locked up or kept by someone other than the researcher. It does not matter if the tissue would otherwise have been discarded. You should be aware that many institutions require an IRB to determine whether or not the research is exempt.

What is meant by "existing" data or specimens?

Exemption #4 applies to retrospective studies of specimens that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is initiated. For research supported on NIH grants and contracts, the specimens should be in place at the time the proposal is submitted for review.

What about specimens obtained from a tissue bank?

Use of tissue specimens obtained from an established tissue repository may be exempt, even though the bank continues to procure new specimens while the research project proceeds. There are many kinds of tissue banks that operate in different ways. Your IRB will need to determine whether the bank you are using meets the requirements of the exemption.

What is meant by "publicly available sources"?

This language in the regulation was intended to apply to public sources of *data*, such as death certificates. Its meaning with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible at reasonable cost to the research community, these materials are not usually available to the public at large. Even if you obtain specimens from such a source, you should not assume that it meets the definition of "publicly available." It is up to your IRB to decide.

What is meant by "identifiers linked to the subjects"?

Identifiers such as names, Social Security numbers or pathology accession numbers permit specimens to be linked to individual people and perhaps also to associated medical information. Exemption #4 applies most clearly to specimens where such personal information was never collected. It may apply to specimens provided by a tissue bank or other repository, so long as the specimens are provided without identifiers and the repository has firm policies and procedures, reviewed by its own IRB, to prevent the release of personal information. **It generally does not apply in situations where a researcher receives "coded" specimens from a collaborator if the collaborator retains the key to the code, even though the researcher may have no access to patient identities.**

How can I determine if my research is exempt?

The humans subjects regulations decision charts from the Office of Protection from Research Risks (OPRR) (available from their website at: http://www.nih.grants/oprr/humansubjects/guidance/decisioncharts.htm) will help you to see whether your research falls under the human subjects regulations and if so, whether it is likely to require full IRB review or is a candidate for expedited review. You should be aware, however that institutions vary in their requirements for IRB review. **Many institutions require some form of IRB review for exempt studies. You must check with your institutional officials to determine whether full, expedited, or no IRB review is required for your proposed project.**

IF I OBTAIN ALL MY SPECIMENS FROM COLLABORATORS, DO THE REGULATIONS APPLY?

YES! Unless your research is exempt, BOTH you and your collaborator must have approvals from the IRBs at your respective institutions.

What if my collaborator is located outside the U.S?

Your collaborator will need to obtain approval from the IRB at his or her institution. In addition, your collaborator's institution will probably need to contact OPRR and provide documentation that its IRB meets the requirements defined in U.S. laws. An assurance coordinator at OPRR can assist you with this process. Finally, your NIH program official may need to request State Department clearance for your project.

The key is: start early! Obtaining approvals and assurances takes time, particularly if institutions are located overseas. No NIH grant or contract can be awarded until the necessary approvals and assurances are in place.

WHAT KEY POINTS SHOULD I ADDRESS IN MY RESEARCH GRANT APPLICATION OR CONTRACT PROPOSAL TO THE NIH?

The PHS 398 application kit for a Public Health Service grant (http://grants.nih.gov/grants/funding/phs398/phs398.html) requires information about the involvement of human subjects in the proposed research. The face page of the application asks you to certify whether or not human subjects are involved, and, if so, whether an exemption is claimed and the exemption number. In the case of a research contract proposal the Optional Form 310 will serve in lieu of the PHS 398 Form. If your institution has an applicable Multiple Project Assurance on file with OPRR, and the research is not exempt, you or your business office must provide an Assurance of Compliance Number, the IRB approval date, and indicate whether the approval was by full IRB review or by expedited review. If your proposal is selected by the NIH for an award and your institution does not have a Multiple Project Assurance, then it must contact OPRR.

Additional information must be provided in the Human Subjects section of the Research Plan. If you have claimed an exemption on the face page (or on Optional Form 310 for a contract proposal), you should provide sufficient information in the Human Subjects section and in the body of the proposal to show that the exemption is appropriate. It is important to state whether the specimens already exist or will be collected prospectively and whether the specimens can be linked to subject identifiers.

This information should be provided for all specimens, including those obtained from collaborators. (Include the letters of collaboration with your proposal, rather than placing them in the Appendix.) Also remember that any NIH grant application or contract proposal involving human subjects must address the inclusion of women, minorities and children. Failure to provide this information could delay or prevent the award of your grant or contract.

The NIH Scientific Initial Review Group will review the information you provide in the grant or contract proposal to determine whether plans and approvals for use of human subjects are appropriate. Any comments or concerns noted by the Scientific Review Group are transmitted to the NIH awarding unit, institute/center's council and the OPRR. The NIH awarding unit staff, in consultation with OPRR, are responsible for ensuring that any human subjects concerns are resolved prior to funding. NIH staff members are responsible for ensuring on an annual basis that there are no major changes in the human subjects research and that annual IRB approvals are obtained.

From time to time changes are made in the human subjects regulations and in their interpretation by IRBs and by OPRR. It is important to thoroughly review and understand the most current regulations before submitting your grant application and particularly before starting research. Check with your local IRB for guidance.