How the Human Subjects Regulations Apply to the use of Specimens for Research

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Are you conducting research using human subjects?

A **'human subject'** is a living individual about whom an investigator obtains either data through intervention or interaction with the individual, or 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 conducting human subjects research, you must…

…comply with your institution's rules and the requirements of your Institutional Review Board (IRB)[2] and meet Federal requirements 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. 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 46.102(e)

[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 IRB elsewhere that satisfies all Federal requirements. For more information about these options contact the Office for Human Research Protections.

What is the role of my institutional review board?

The IRB at your institution must review and approve research if it involves human subjects. The IRB review process serves to protect the rights and welfare of human subjects by minimizing risks, selecting subjects equitably, obtaining informed consent (when required) 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 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 the adequacy of privacy and confidentiality protections.

Does my research involve "human subjects" or is it exempt from IRB review?

Research with specimens and data from living persons does not require IRB approval either when it is determined that the research does not involve human subjects as defined in the Code of Federal Regulations (CFR) at Title 45 Part 46.102(e), or when it is determined that the only involvement of human subjects is in one of the "exempt" categories listed at 45 CFR 46.104(d).

The Office for Human Research Protections (OHRP), the organization which oversees implementation of the Federal Human Subject Protection Regulations, has issued guidance about determining when research with coded biospecimens or private data involves a "human subject", or is exempt from the regulations.

[3] Title 45 Code of Federal Regulations, Part 46.116(f)

According to this guidance, researchers who obtain coded specimens that cannot be linked to specific live individuals are **not** conducting research involving a "human subject".

For example, if there is an agreement between a researcher and a specimen provider for the transfer of coded biospecimens which prohibits the release of the code key, the specimens are not considered individually identifiable and the specimen provider, without additional collaboration in the research, is not considered engaged in human subjects research. Similarly, in the case of coded specimens obtained from a biobank or university, if there are institutional operating policies or other legal requirements prohibiting release of the code key to the researcher, the specimens are not considered individually identifiable, and the researcher is not considered engaged in human subjects research. Under these circumstances, informed consent might not be required to conduct research using the coded specimens. However, most research institutions, including NIH, require investigators to obtain human subject review of research involving coded specimens to ensure that all appropriate protections have been provided.

A regulatory exemption that is most pertinent to work with human tissue specimens is described at 45 CFR 46.104 and applies to existing specimens and data:

> *"(a) Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories in paragraph (d) of this section are exempt from the requirements of this policy, except that such activities must comply with the requirements of this section and as specified in each category[...]*
>
> > *"(d)(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:*
> >
> > > *"(i) The identifiable private information or identifiable biospecimens are publicly available;*
> > >
> > > *"(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;"*

Some researchers mistakenly believe that any studies on existing pathology specimens are exempt. However, the 45 CFR 46.104(d)(4)(ii) exemption does **not** apply to specimens that can be 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. In addition, this exemption only applies to specimens that are already "on the shelf" (or in the freezer) at the time the protocol is initiated.

You should be aware that many institutions require an IRB to determine whether the research is exempt or whether specimens have been de-identified. Studies[4, 5, 6] have demonstrated the possibility of re-identification of de-identified specimens and data maintained in aggregate databases such as the NIH database of genotypes and phenotypes (dbGAP)[7]. While the science is evolving rapidly in this area, research specimens are generally considered de-identified under 45 CFR part 46 if there is no data attached (i.e., remnant clinical tissue). Under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, removing eighteen specified types of identifiers from data (such as dates and medical record numbers) makes information de-identified under HIPAA standards.

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.

How can I determine if my research requires prior IRB review?

The humans subjects regulations decision charts from OHRP will help you understand whether your research involves human subjects and if so, whether it is likely to require full IRB review or is a candidate for expedited review. However, institutions vary in their requirements for IRB review and many institutions require some form of IRB review even 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.

What key points should I address in my research grant application or contract proposal to the NIH?

The G.220 - R&R Other Project Information Form and the G.500 - PHS Human Subjects and Clinical Trials Information Form require information about the involvement of human subjects in proposed research. You will certify whether human subjects are involved, and if so, whether an exemption is claimed and the exemption number. If your institution has an applicable Federalwide Assurance (FWA) number on file with OHRP and the research involves human subjects and is not exempt, you must provide the Human Subject Assurance Number, the status of IRB review (i.e., if the review is pending), and the IRB approval date (if review is complete). If your proposal is selected by the NIH for an award and your institution does not have

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[4] Homer N, Szelinger S, Redman M, et al. Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. *PLoS Genet*. 2008;4(8):e1000167. Published 2008 Aug 29. doi:10.1371/journal.pgen.1000167

[5] Jacobs KB, Yeager M, Wacholder S, et al. A new statistic and its power to infer membership in a genome-wide association study using genotype frequencies. *Nat Genet*. 2009;41(11):1253-1257. doi:10.1038/ng.455

[6] Im HK, Gamazon ER, Nicolae DL, Cox NJ. On sharing quantitative trait GWAS results in an era of multiple-omics data and the limits of genomic privacy. *Am J Hum Genet*. 2012;90(4):591-598. doi:10.1016/j.ajhg.2012.02.008

[7] http://www.ncbi.nlm.nih.gov/gap

an approved FWA on file with OHRP, the organization must comply with 45 CFR 46 and proceed to obtain an FWA.

If you have claimed an exemption, you should provide sufficient information 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. Remember that any NIH grant application or contract proposal involving human subjects must address the inclusion of women, minorities and individuals across the lifespan (e.g., children or older adults). Failure to provide this information could delay or prevent the award of your grant or contract.

The NIH Scientific Initial Review Group (SRG) 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 SRG are transmitted to the NIH awarding unit, institute/center's council and the OHRP. The NIH awarding unit staff, in consultation with OHRP, 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 OHRP. 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 IRB for guidance.

Where can I find help and additional information?

- Your institution's IRB
- The Office for Human Research Protections (OHRP)
- Your NIH institute/center Program Official
- Office of Science Policy (OSP) Clinical Research Policies
- NHGRI Policy Issues in Genomics