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Introduction to Biospecimens

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With the growth of personalized medicine, biospecimen collection has become a common component of clinical trials. It is important, therefore, for clinical researchers to consider issues related to the collection and storage of samples, such as: why biospecimens are collected, how the regulations apply to tissue collection and storage, what information should be included in the informed consent document, and whether or not test results, including incidental findings, will be revealed to study participants.

After collection, biospecimens, sometimes referred to as "tissues," "specimens" or "samples," are stored in a tissue bank. A "tissue" is a specialized set of cells, e.g., liver tissue, tumor tissue, or blood. A specimen is a piece of tissue. A sample is a portion of a specimen. A tissue bank, also called a "repository," "biorepository" or "biobank," is a facility that receives, stores, processes and/or distributes tissue collections.

Tissue Bank Types, Purposes and Characteristics

A tissue bank can be either a "population" bank or a "clinical" bank. A population bank is a biorepository for which specimens are collected from a large number of subjects. Samples stored in a population bank may be categorized according to characteristics like age, gender, race, residence, exposures and other general lifestyle traits. Scientists can study the specimens in a population bank to answer a wide variety of questions that were not anticipated when the specimens were collected. In contrast, clinical tissue banks specialize in a specific disease, e.g., lung cancer, so they typically contain specimens from people with that particular disease.

The primary purpose of a repository may be related to clinical care, e.g., to measure the progress of a disease, or it may be aimed at current or future research. While a tissue bank might be created for a clinical trial, a fundamental property of biospecimens is that they can be useful in ways that cannot be anticipated when they are collected.

There are numerous variables in the function and organization of tissue banks. Tissues stored in a particular repository may be from the general population, a group of people with a specific disease, or participants in a clinical trial. Repositories also vary according to who may access specimens, the scope of banked material, and whether the bank is a single-site repository or part of a network of repositories. Some tissue banks allow only researchers affiliated with one institution to access samples, while other banks also allow access to external researchers. The way samples are identified also varies. Samples may be stored or distributed with the donor's name attached, with a coded identity, or completely anonymously.

Biospecimens can be used in research in a variety of ways. They may be studied to confirm a diagnosis or to evaluate response to a treatment. In oncology, the examination of tumors is an essential way to learn more about the biology of cancer. By studying tissues, researchers can link abnormalities in a tissue to the cause, prognosis and efficacy of a particular treatment. It may be possible to test a treatment (or a large number of potential treatments) on biosamples before testing it on human subjects.

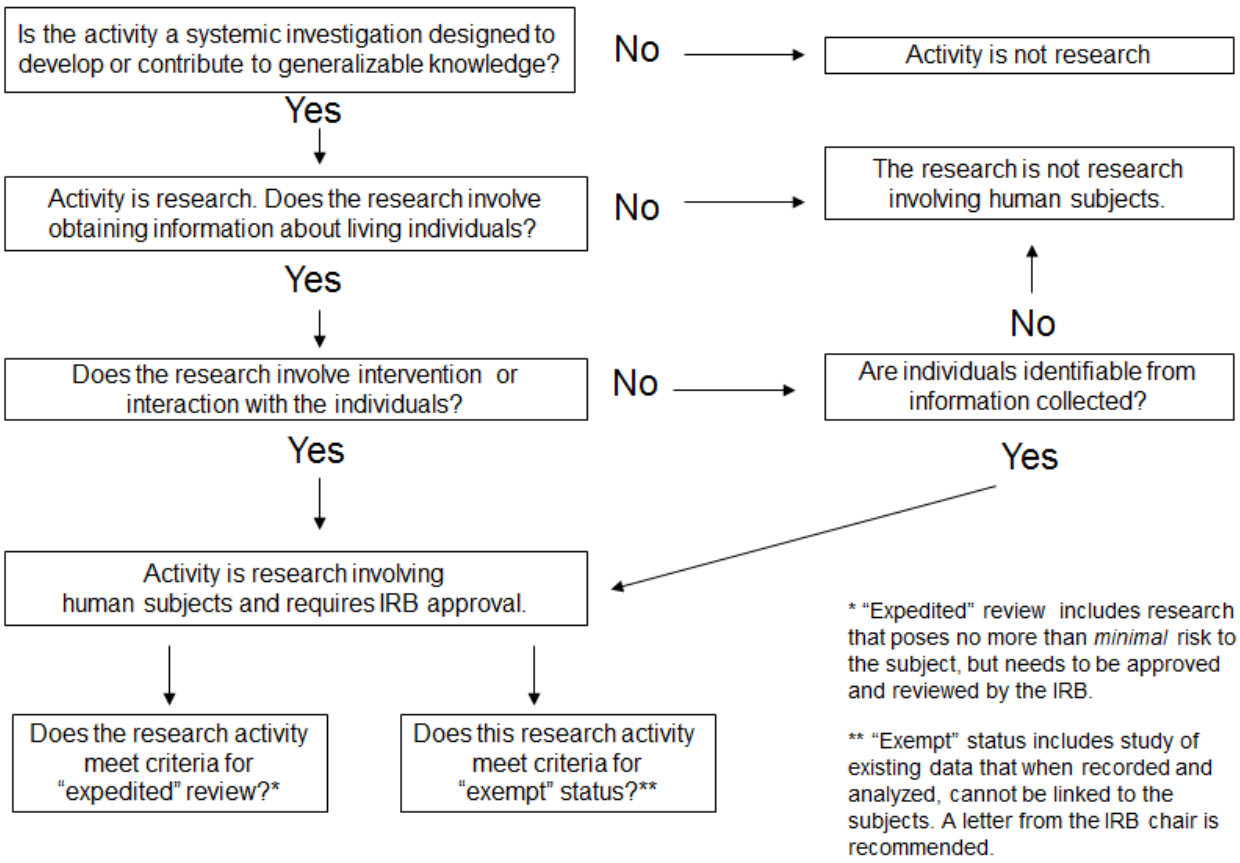
Ethics and Regulations

Tissue banks should adhere to the ethical principles of the Belmont Report: respect for persons, beneficence and justice. Individuals donating samples to a repository should do so voluntarily, with a clear explanation of the reason the samples are being collected. Donors should be aware of any potential social, psychological and/or financial risks of donating tissue. The benefits and burdens of tissue research should be distributed equitably.

The research team should know when and how to apply the Common Rule (45 CFR 46) to its tissue bank. There are three primary questions:

- Is it research? Is the tissue going to be analyzed in such a way that the investigation meets the definition of research in 45 CFR 46.102(d)?
- Does the research involve human subjects? Will data be collected through interaction or intervention with living individuals OR will identifiable private information be collected?
- Does this study meet the criteria of exempt research as described in 45 CFR 46.101(b)(4)? If the samples are collected and stored in such a way that subjects cannot be identified directly or through identifiers linked to them, the research may be exempt. However, it is up to the IRB and not the investigator to determine if a protocol meets the criteria for exemption. Figure 1 provides an algorithm that can be used to help determine whether or not a study involves human subjects:

Figure 1. Does A Study Involve Human Subjects?



Informed Consent

Elements of informed consent for tissue bank research apply when a study qualifies as human subjects research. In addition to the usual elements of consent, biospecimen informed consents should include the following topics:

- The purpose(s) of collecting and storing the samples
- How the specimen(s) will be stored and for how long
- Whether refusal to donate specimen(s) will prevent the subject from participating in the study
- Whether the subject will be told of any results from studying the specimen(s)
- Whether the subject can withdraw consent for the tissue research protocol and still stay in the main study
- Who will have access to the specimen(s) and associated data
- Whether the subject will need to consent to future use or distribution of the specimen(s)
- Who will be the custodian of the specimen(s) and associated data
- Whether the participant will benefit from any financial benefit that might result from research on the specimen(s)

As with all informed consents for research studies, biospecimen consents should clarify, to the extent possible, the risks and benefits associated with the study. Genomic testing carries its own unique risks, such as exposure of heritable family traits, questions of paternity, test results that could affect other family members, and stigmatization. Topics that should be addressed include:

- Will identifiers be linked to the samples?
- What is done with the extra tissue?
- Will participants be informed of test results?
- How might family members be affected by test results?

Consent forms for biospecimen research usually fall into one of four models:

- A "specific" consent is one that pertains to a specific project. The specimen will be analyzed only in that particular study. Specific consents limit the type of research for which a specimen can be used and may prohibit future research.
- A "broad" consent may be obtained for a specific study, but it also allows certain future research, generally in the same area as the original study.
- A "blanket" consent has few, if any, limitations on usage of biospecimens.
- A "dynamic" consent requires the donor to consent to each use of a biospecimen.

Options for future use of a biospecimen after a clinical study may be incorporated in the main consent form. The subject may be asked to choose one of the following options:

- My sample may be used for future research on <specific disease>.
- My sample may be used for future research on diseases related to <specific disease>.
- My sample may not be used for future research unless the researcher first contacts me and obtains my approval.
- My sample may not be used for future research. Do not contact me about this in the future.

Subjects may also be given the choice of not receiving the results of biospecimen testing, with the alternative to opt out of disclosure clearly stated in the informed consent form.

Privacy

As with all clinical trials, biospecimen researchers must protect the confidentiality of identifiable information. Protections might include coding or anonymizing the samples, encrypting and/or limiting access to related data, or use of a third-party "honest broker" to protect the subjects' samples and/or identity.

The informed consent form should explain how the subject's privacy will be protected. It should clearly state if individual or aggregate research results will be revealed, and if so, to whom (e.g., the subject, the subject's healthcare provider, family members, other researchers, public health officials), and how the information will be communicated.

Incidental Findings

When considering whether to reveal test results to study participants, particular attention should be paid to incidental findings, i.e., findings uncovered in the course of conducting the research that is beyond the scope of the research study. For example, a study on a biospecimen from an apparently healthy volunteer might reveal high susceptibility to a particular cancer or a gene that might cause a birth defect in offspring.

Questions investigators should consider before engaging in tissue research include the following:

- Will subjects be informed if future tests reveal clinically significant information?
- What type, if any, of incidental findings will be revealed to the subjects?

The National Bioethics Advisory Committee (NBAC) recommends disclosure of results when:

- The findings are scientifically valid and confirmed,
- The findings have significant implications for the subjects' health concerns, and
- A course of action to ameliorate or treat these concerns is readily available.

The pros of revealing findings include the fact that, when applicable, the research subjects are competent adults who are entitled to the information and self-determination. The cons may be that not all labs are CLIA compliant, the significance of the results is unclear, or acting on unvalidated findings might subject the study participant to unnecessary and even harmful medical interventions.

Ownership

Another issue related to tissue banking and research is: Who owns the tissue? When tissue donors have sued for some of the financial gain that has resulted from the research performed on their tissue, the courts have ruled, in all but one case, in favor of the defendants, declaring that once a subject donates a biospecimen, the individual no longer owns the tissue and is not entitled to any profits that have resulted from studying the tissue.

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