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WHITE PAPER

Recommendations to Consider When Sourcing Human Biospecimens

Ethical Considerations in Human Biospecimens

The foundations for protecting human research subjects come from the ethical principles surrounding the Belmont report : Respect for persons, beneficence, and justice. The use of human biospecimens in research supports these principles with legal and ethical regulations - the most important of which is permission.[1] This permission may come directly from the donor or granted by others with authorization to protect the interests of biospecimen donors.

- In the United States (US), Institutional Review Boards (IRBs) are responsible for the regulatory oversight of research involving human research subjects. Office of Human Research Protection (OHRP) 45 CFR Part 46 regulations governs IRBs.
- In other countries, the Ministries of Health (MOH) or their equivalent may be responsible; or may transfer the responsibility to authorized Independent Ethics Committees (IECs). They are typically directed by the Nuremberg Code, Declaration of Helsinki and guidelines established by the Council for the International Organization of Medical Sciences (CIOMS) and the principles of Good Clinical Practice (GCP).

In addition to being responsible for reviewing research and the regulatory maintenance of research, IRB/IECs determine if research is considered human subject research and if informed consent will be required. Human subjects are defined per 45 CFR 46.102(f) as a living individual about whom an investigator conducting research obtains 1) data through intervention or interaction with the individual, or, 2) identifiable private information.[2]

Informed Consent

Informed consent is the understanding, and written acceptance of the research, its risks, benefits, and use of specimens, and data gathered as a result of the research. Participants must receive adequate information to make an 'informed' decision. For studies that involve the collection of biological specimens, recommended components of the informed consent document include:

- Purpose of study, study procedures, risks and discomforts, benefits or participation, compensation and/or reimbursement for participation if applicable, and information regarding voluntary withdrawal.
- A general statement regarding the end use of specimens and data at the time of collection as the knowledge of the specific current and future use of the samples may not be known. The general statement may include that samples could be used in the development and improvement of new diagnostic test kits, devices, biomarker discovery, or general research on particular diseases and illnesses.
- A statement regarding the potential commercial use of samples and data. Specimens provided may result in new products, tests, or discoveries that may have commercial value. There is no intention to share the monetary benefits from these products, tests, or discoveries. Caution must be met when speaking of commercialization of biospecimens in the world arena, as there is cultural skepticism.
- Inclusion that study results may appear in journals, academic papers, etc., and an assurance that identifying data will not be published.
- Information regarding the storage and future use of samples and data. How many years are the samples expected to be stored? Will data and samples be stored for an indefinite period of time?
- Requirement to inform subjects if their samples will undergo genetic testing or if such testing is optional (in rare cases). In the US, GINA (Genetic Information Nondiscrimination Act) recommends language indicating that genetic information resulting from the study will not result in discrimination.
- In the US: Statement on the use of protected health information (PHI) such as demographics and medical history data, including who would have access to their information and how this information will be used, including in the future. This section is also known as HIPAA authorization. The Health Insurance Portability and Accountability Act (HIPAA) requires that covered entities obtain authorization or waiver of authorization for the use and disclosure of PHI (45 CFR 164.508).

  In the EU: THE EU General Data Protection Regulation (GDPR) while extending beyond the sourcing of human biospecimens, impacts the personal data collected by any donor. This regulation, with enforcement beginning May 25, 2018, harmonizes data privacy laws across Europe and offers protection and empowerment to all EU citizens in terms of data privacy.

Demystifying Donor Reimbursement

Subject compensation and reimbursement continues to be a highly debated topic due to the possibility of coercion and undue influence. Compensation is considered payment for time, inconvenience, discomfort, etc., whereas reimbursement is considered payment for travel expenses such as mileage, airfare, lodging, etc. In the U.S., donor compensation is acceptable for research participation, but requires review at time of IRB approval that it does not impart undue influence on the participant. The IRB addresses sponsor and investigator proposed compensation amounts for research subjects and the specific details regarding what compensation is provided for. The IRB also reviews the method and timing of payment. All information regarding payment, including the amount and timing of payment, should be detailed within the informed consent. In the EU, the European Commission has set out in Directive 2004/23/EC that "Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted."[4]

Thus, each country has its own level of compensation and/or reimbursement acceptability and this should be taken into consideration when sourcing biospecimens. Some countries may not allow payment for study participation or reimbursement for reasonable travel and lodging expense. In this case the informed consent would include such details.[4]

Frequently Requested Biospecimens

The most commonly requested tissue and biological fluids (collectively biospecimens) can be categorized by their method of sourcing in the following manner:

- Prospective
- Retrospective (a.k.a. excess, leftover, library, residual, etc.)
- Post Mortem

Prospective collections require subject informed consent. During the informed consent process subjects must provide written authorization to donate their specimen and data for research purposes according to specified requirements. The specimens may be additional samples collected from a procedure subjects are already undergoing for standard of care or collected specifically for research (such as blood).

Retrospective or remnant samples do not require subject informed consent. Under the definition of human research subject [45 CFR 46.102(f)], OHRP does not consider research involving only coded private information or biospecimens(retrospective or remnant to involve human subjects. Meeting both the following conditions would, therefore, waive the requirement for documented informed consent:

- The private information or specimens were not collected specifically for the currently proposed research project through interaction or intervention with living individuals; and
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain.[5]

In the U.S., deceased subjects (cadavers) are not considered human research subjects according to existing regulations. Hence, IRBs do not review post-mortem research. For this reason, federal and state laws, including HIPAA, should be referenced when procuring samples from cadavers. The Uniform Anatomical Gift Act (UAGA), adopted in some form by all 50 states of the U.S. and the District of Columbia (DC), gives individuals the right to make written directives that allow the donation of their bodies and organs for transplantation or science. The UAGA allows, in the absence of such a written directive, next-of-kin authorization of the gift. These documents should be available when sourcing post-mortem samples.

Quality Considerations in Human Biospecimens

Originally, biobanks were used to store archival specimens from in-house longitudinal studies (such as the Framingham Study). These specimens were collected, processed, and stored according to each institution's procedures. As research began to focus on biotherapeutics and personalized medicine, scientists identified a need for high-quality human specimens with detailed clinical data. In addition, researchers were seeking large numbers of specimens and data to obtain statistically significant results.

As researchers worked with various biobanks, it became apparent that the specimen quality was highly variable. Not all facilities were obtaining the right type of consent, capturing meaningful clinical data, processing the specimens using the same techniques, or storing specimens in the right conditions.

As a consequence of the various issues discussed above, various research groups identified the need to define standards of processing for reliable specimen quality:

- International Society for Biological and Environmental Repositories (ISBER) is a global biorepository organization established in 1999 to focus on identifying and harmonizing "quality standards, education, ethical principles, and innovation in the science and management of biorepositories".[6] ISBER first published its Best Practices in 2005 to recommend the most effective practices for specimen collection, storage, retrieval, and distribution.
- National Cancer Institute (NCI) established a Biorepository Coordinating Committee in 2004-2005 to identify and resolve biospecimen resource issues. This led to the publication of the NCI Best Practices for Biospecimen Resources on April 28, 2006.
- The consensus of the ISBER, NCI, as well as the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) and European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) groups are the basis for current biorepository standards and principles that meet the global research needs for high-quality biospecimens.

"We believe that patients and families will have more confidence that their wishes will be respected, that organs and tissue used in treatment will be safe and high quality; and that tissue used for research or other purposes will be put to the best possible use, if they know there is regulation of human tissue and organs."

UK Human Tissue Authority

Research frequently requires large numbers of samples with adequate specimen size and volume. Consistent sample quality is expected with a range of sample types that are representative of the condition(s) being studied. In addition, researchers are looking for clinical data and demographics to accompany the samples and support their research. The reliability of data derived from human specimens is dependent on the quality and consistency of the analyzed sample.

Due to the importance of sample quality, associated data, and proper consent, certain criteria should be discussed when selecting a CRO or biorepository to conduct specimen collections on behalf of research.

First, a CRO/biorepository should have defined quality criteria for both biospecimens and associated data. This includes identifying the minimum sample standards for size, volume, and appearance. Specific accompanying test and laboratory reports to case report forms should be utilized for data capture to confirm accuracy. Confirmation of sample diagnosis in correlation with clinical data by a board-certified pathologist ensures that each specimen meets product quality standards, confirms tissue origin and diagnosis, and verifies sample data quality and integrity.

In addition, defined specimen retrieval and processing procedures must be in place to ensure specimen integrity is maintained. Samples storage conditions need to be defined for each specimen type, with temperature conditions for maintaining sample integrity from collection, to storage, processing, and shipment. All instruments and equipment need to be properly operated, maintained, serviced, and monitored.

All related technical policies and procedures to ensure defined specifications should be documented, including authoring and review by personnel with knowledge of CRO/biorepository requirements. These documents should be controlled so that only current policies and procedures are in use by all personnel.

Sponsor audits of donor sites will further ensure the collections sites are following sponsor instructions and IRB approved protocols, and adhering to the highest ethical standards.

In order to best utilize human specimens for research, the purpose and the types of collections required to meet the research needs should be identified at the time of sourcing. This will enable recommendations on sourcing the required biospecimens according to relevant regulatory and ethical standards. It is important to remember that one type of collection is not necessarily better than another, but that there are variables in place that require different collection procedures. The following three points are a high-level summary of the three main types of collection, prospective, retrospective and post-mortem.

- Prospective sample availability may be limited (if samples are not available in stored inventory). However, prospective collection may allow researchers to control the conditions under which a sample is collected and obtain required data, with follow-up arranged if necessary for further data accrual.

- Retrospective samples may be more accessible; however, data may be limited and collection and processing conditions may not be known.

- Post-mortem samples are good sources for many biospecimens but may not have the documentation or data required. The viability of post-mortem samples may also be a matter of concern.

Summary

The biobanking landscape and biological specimen use in research are continually evolving. In response to the drive for continuous improvement, both government and medical professional societies have instituted regulations or accreditation programs to facilitate best practices. Specifically, the Human Tissue Authority was established in the United Kingdom to regulate organizations that "remove, store and use human tissue for research, medical treatment, post-mortem examination, education and training, and display in public". [7] Furthermore, the College of American Pathologists (CAP) has initiated a Biorepository Accreditation program. [8] This program, "designed to improve the quality and consistency of facilities that collect, process, store and distribute biospecimens for research"[3], is cited as a reference for the best practices by the National Cancer Institute.

BioIVT, with its ASTERAND™ Human Tissue facility being CAP Biorepository accredited since 2012 and UK facilities being HTA licensed, is committed to staying abreast and adopting new standards as they are established to achieve consistency of biospecimen quality. Please feel free to contact us for additional information regarding our capabilities, or with additional questions concerning the ethical and quality-ensured collection of human specimens.

BioIVT, formerly BioreclamationIVT, is a leading provider of control and disease state samples (human/animal tissues, cells, blood, other biofluids). Our PHASEZERO® team provides value-added services that evaluate the efficacy and safety of therapeutics. Combining technical expertise, exceptional customer service, and unparalleled access to biospecimens, BioIVT partners with scientists in ELEVATING SCIENCE™.

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(1) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. [Bethesda, Md.]: The Commission.
(2) https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.102
(3) Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
(4) https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm HTA Human Tissue Authority, https://www.hta.gov.uk
(5) https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html
(6) www.isber.org
(7) HTA, Human Tissue Authority, https://www.hta.gov.uk
(8) CAP Biorepository Accreditation Program http://www.cap.org/web/home/lab/accreditation/biorepository-accreditation-program