Consent and Biospecimen Collection in Human Research

Legal and ethical regulations have to be enforced when using human biospecimens in research. Ensuring researchers have the authorisation to use biospecimens is vital

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Regulations governing the protection of human research subjects are based on the ethical principles identified in the Belmont Report: "respect for persons, beneficence, and justice" and in the Nuremberg Code and the Declaration of Helsinki (1-3). Guidelines established by the Council for the International Organization of Medical Sciences, the Nuffield Council on Bioethics, and Good Clinical Practice also contributed (4-6). The application of these principles in the use of human biospecimens in research is enforced by legal and ethical regulations, the most important of which relates to permission. This may come directly from the donor or be granted by others with authorisation to protect the interests of biospecimen donors.

Legal and ethical oversight is country/region-specific. In the UK, consent or authorisation is required for the collection of biospecimens for research from both living and deceased donors, with a similar situation existing in other European countries. However, in the UK, whether or not a research study also requires ethical approval by an independent ethics committee (IEC) can be determined via an online tool provided by the Health Research Authority (7). In the US, institutional review boards (IRBs) are responsible for the regulatory oversight of research involving human subjects, with the Office of Human Research Protection (OHRP) 45 CFR Part 46 regulations governing IRBs and their operation (8). In other countries, the ministries of health (MOH) or their equivalent may be responsible or may transfer the responsibility to authorised IECs.

Informed Consent

Informed consent is written acceptance to participate in a research project based on an understanding of the aims of the research, its risks and benefits, and the planned collection of specimens and data for research purposes. Participants must receive adequate information to make an 'informed' decision, including the opportunity to ask questions. For studies involving the collection of biological specimens, recommended components of the informed consent document include:

- A description of the study purpose, procedures, risks and discomforts, benefits of participation, and information regarding voluntary withdrawal
- A description of the proposed use of the specimens and data, as far as is known at the time of collection. This may include use of the samples in development and improvement of new diagnostic test kits/devices, discovery of new biomarkers, discovery/development of new drugs or other therapeutic agents, or general research on specific diseases and illnesses. The amount of detail required here varies from one jurisdiction to another. In the US, the statement may be quite broad and need not describe a specific project using the samples. In the UK and many other European countries, ethical committees require more specifics on the proposed use and may also require return of any unused samples at the end of the specified project
- A summary of the potential use of samples and data in both for-profit and non-profit settings. It should also state that this research may eventually result in new products, tests, or discoveries with commercial value and should include a clear statement that any monetary benefits arising from these products, tests, or discoveries will not be shared with donors of samples/data used in their development
- A statement that study results may be reported 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. This should include a statement that donor privacy will be safeguarded with appropriate security measures and state how long the samples are expected to be stored
- A statement informing subjects whether their samples may undergo genetic testing or if such testing is optional (in rare cases)
- Compliance with the General Data Protection Regulation, which applies to personal data collected for any person, including donors of human biospecimens. This regulation, which came into effect on 25 May 2018, harmonises data privacy laws across Europe and offers protection and empowerment to all EU citizens in terms of data privacy (9)
- A statement regarding any reimbursement or compensation payments to the donor, including the amount and timing of payments

Frequently Requested Biospecimens

The most commonly requested tissue and biological fluids (collectively referred to as biospecimens) can be categorised by their method of sourcing in the following manner:
- Prospective
- Retrospective
- Post-mortem

Prospective Collections

These include: excess material collected from a procedure that the subject is already undergoing for standard of care (for instance, material surgically removed as part of treatment or the remains of diagnostic samples left after diagnosis is complete) or extra samples collected specifically for research, for example, additional blood. In most countries, prospective collection of specimens and data for research use requires the donor's written informed consent.

Retrospective or Remnant Samples

Retrospect or remnant specimens are those which are not collected with research in mind, but left over after diagnostic tests and analyses have been conducted, for example, archival pathology blocks or other laboratory test remnants.

In the UK, archival tissue can be legally used in research without consent or outside the terms of the original consent, if certain legal exceptions apply (10). These circumstances differ between UK countries.

England, Wales, and Northern Ireland
Research without consent is possible if the samples were taken from a living person, are anonymised to the researcher, and an NHS Research Ethics Committee (NHS REC) has approved it. The approval must be project-specific andmust include the use of the samples without consent. For this exemption to apply, an NHS REC must be convinced that the use of the samples is ethical and appropriate. Alternatively, samples that have been in the archive since before the Human Tissue Act 2004 came into effect (ie, before 1 September 2006) can be used for research without consent. However, such samples should be anonymised to guard against any breach in confidentiality.

Scotland
The legal need for consent applies only to tissue removed from the deceased for research or 'bodily material' if it is held with the intention of analysing its DNA. The legal exemptions to the need for consent in these cases are as follows:

- Tissue from the deceased: Samples collected prior to 1 September 2006 can be legally used for research without consent, although use of whole organs requires NHS REC approval regardless of when the samples were collected
- Bodily material held with the intention of analysing its DNA: Consent is not required if the samples were collected prior to 1 September 2006 or if they were taken from the living and are robustly anonymised to the researcher (eg, by coding) and an NHS REC has given project-specific approval which includes the analysis of DNA.

In the US, such retrospective/remnant samples may be used for research without the donor's informed consent under two circumstances:

1. An IRB may waive the requirement for informed consent if certain conditions are met
2. Alternatively, under the definition of human research provided by the OHRP, research involving only coded private information or specimens is not deemed to involve human subjects as defined under the 45 CFR 46.102(f) regulation and may be considered exempt from IRB review

In general, each country or region may have its own regulations regarding the use of retrospective or remnant samples. Working closely with the IEC or MOH and other regulatory bodies should make certain that the appropriate actions are being taken to ensure ethical procurement of human biospecimens.

Post-Mortem Collections

In the UK and Europe, post-mortem samples are regarded as gifts, and their use in research is regulated in a manner similar to samples from living donors (11). In the UK, removal of tissue from the deceased for research must always take place under the authority of a human tissue authority (HTA) licence, and the tissue may only be retained for use in research if appropriate consent has been obtained either from the donor or from their next of kin. Tissue for research must also be stored on HTA-licensed premises.

In the US, deceased subjects (cadavers) are not considered human research subjects according to existing regulations. For this reason, federal and state laws, including The Health Insurance Portability and Accountability Act of 1996, should instead be referenced when procuring samples from cadavers.

Quality Considerations

Originally, biobanks were used to store archival specimens from in-house longitudinal studies (such as the Framingham Heart Study [12]). As research began to focus on biotherapeutics and personalised medicine, scientists identified a need for high-quality human specimens with detailed clinical data. Additionally, researchers were seeking large numbers of specimens and data to obtain statistically significant results. As researchers worked with differing 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 these issues, various research groups identified the need to define processing standards to ensure reliable specimen quality:

- The International Society for Biological and Environmental Repositories (ISBER) is a global biorepository organisation established in 1999 to focus on identifying and harmonising "quality standards, education, ethical principles, and innovation in the science and management of biorepositories" (13). The ISBER first published its best practices in 2005 to recommend the most effective practices for specimen collection, storage, retrieval, and distribution. The latest edition of this reference was published in 2018
- The US 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 in 2006; the most recent edition is dated 2016 (14)

The consensus of these two organisations, as well as the Biobanking and Biomolecular Resources Research Infrastructure, the UK HTA, and the European, Middle Eastern, and African Society for Biopreservation and Biobanking, provides the basis for current biorepository standards and principles that meet the global research needs for high quality biospecimens (15-17).

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. Additionally, researchers are looking for clinical data and demographics to accompany the samples and support their research. The reliability of data derived from human specimens depends on the quality and consistency of the analysed samples.

Due to the importance of sample quality, associated data, and proper consent, several criteria should be considered when selecting a CRO/biorepository to conduct biospecimen collections for research. First, the CRO/biorepository should have defined quality criteria for both biospecimens and associated data. This includes identifying minimum sample standards for size, volume, appearance, and quality. Specific accompanying test and lab reports and medical case report forms should be utilised for data capture to confirm accuracy. Each sample should be reviewed by a fully qualified or board-certified pathologist to confirm the tissue origin and diagnosis and verify that the sample and its associated data meet product quality standards.

The Evolving Landscape

The biobanking landscape and biospecimen 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 programmes to facilitate best practices. Specifically, the HTA was established in the UK to regulate organisations that "remove, store and use human tissue for research, medical treatment, post-mortem examination, education and training, and display in public" (16).

Furthermore, in the US, the College of American Pathologists has initiated a Biorepository Accreditation programme (18). This programme, "designed to improve the quality and consistency of facilities that collect, process, store and distribute biospecimens for research" is cited as a reference for the best practices by the US NCI.

References

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